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THE SYSTOLIC MURMUR: FURTHER OBSERVATIONS ON ITS CLINICAL SIGNIFICANCE *

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THE clinical significance and the circulatory dynamic background of systolic murmurs have been subjects of considerable discussion for a great many years and probably will remain so.[1, 2, 3, 4] The interpretations of such murmurs have varied from time to time. Once they were generally recognized as indicative of grave heart disease and later as having no meaning whatever.[5] More recently a middle course has been taken by many of those interested in the subject.[1, 6] The phenomenon is such that careful clinical observation in human beings offers the means of clarifying some of the confusion that exists. For this reason some simple observations on the production of the systolic murmur were made under control circumstances.

Transient systolic murmurs, which may be detected in a number of individuals with presumably normal hearts, can be divided into those which appear during the course of disease, such as hyperthyroidism, anemia, neurocirculatory asthenia, fever, etc. and those which are artificially produced by exercise or the administration of certain drugs.

Several rather extensive studies have demonstrated how frequently systolic murmurs may occur during exercise. Munford [7] found that 7.8 per cent of 1552 students developed heart murmurs after exercise. MacKenzie [7] noted an incidence of 27.8 per cent in 266 apparently healthy students following exercise, while Siemsen [3] has reported the development of murmurs in 46 per cent of a group of 275 children and adolescents. Freeman and Levine [1] were able to produce a systolic murmur of grade 1 or 2 intensity at the apex or base in 9 out of 10 normal persons after exercise and expressed the opinion that systolic murmurs appearing after effort, when not present previously, have no significance and may be found in most normal people.

Since amyl nitrite has been used for the purpose of accentuating or bring-

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ing out latent murmurs of organic origin,[2, 8] it was felt that this drug, which is simple to administer, acts quickly and has no disagreeable after-effects, might be used in an effort to determine the incidence, location, and probable mechanism of transient systolic murmurs artificially produced. Similarly in an effort to study the transient murmurs, which appear during the course of an illness, a group of patients with fever were selected for observations, as well as a small group with various types of anemias.

One hundred patients on the medical and surgical wards of the Peter Bent Brigham Hospital known to have no heart disease were subjected to the inhalation of one perle of amyl nitrite (5 minims) until the full pharmacological effect was obtained. This was usually manifested in about 30 seconds by a feeling of fullness in the head, marked vasodilatation in the face and neck, a rise in heart rate and a fall in blood pressure. Auscultation of the heart, pulse readings and blood pressure determinations were recorded before, during, and after the action of the drug by two observers. All resultant murmurs were graded in intensity according to the classification described by Freeman and Levine,[1] who defined the faintest bruit definitely heard as grade 1, a slightly louder murmur as grade 2 and a murmur of moderate intensity as grade 3, up to grade 6, the loudest possible murmur.

Systolic murmurs were produced in 47 of the 100 cases. This is not in agreement with the findings of Kahler,[2] who claims that amyl nitrite seldom produces murmurs in normal hearts. These murmurs were produced in 48 per cent of the male patients and 44 per cent of the females. The extremes of ages for the entire group ranged between 12 and 57 years. There was, however, no striking difference in the average age of those in whom a murmur was produced and those in whom it was not. In the former the average age was 28.8 years as compared with 30.1 years in the latter group.

The average rise in pulse rate was approximately the same for those who developed murmurs and those who did not, being 54 beats per minute above the initial rate (table 1). This rise is about twice as great as that obtained by Cotton, Slade and Lewis.[9] Similarly all patients, whether developing a murmur or not, exhibited a substantial drop in the systolic and diastolic blood pressure of approximately the same magnitude. Following the subsidence of the amyl nitrite effect, there was usually noted in both groups a rise in blood pressure above the original resting level. In addition the observation was made in those patients developing a murmur, that the murmur frequently appeared as the pulse rate declined and the blood pressure rose above the initial level. From this it follows that the increase in rate is not the deciding factor.

The majority of the murmurs were heard at the base and in practically every instance both observers agreed as to their presence and intensity. In 38 instances a systolic murmur was audible over the pulmonic region, in 16 at the apex and in four over the aortic area (table 2). There were eight patients in whom murmurs were detected both at the pulmonary area and

TABLE I

	Initial pulse rate	Pulse rate during amyl nitrite effect	No. of beats rise during amyl nitrite effect	Initial blood pressure		Blood pressure fall during amyl nitrite effect		Blood pressure rise after amyl nitrite effect	
				Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Cases developing murmurs	77.4	132.7	55.3	124.9	80.1	102.8	53.7	145	92.7
Cases not developing murmurs	82.9	136.6	53.7	124.1	75.2	101.0	53.6	150.8	97.5

apex, two over the pulmonary and aortic regions and one at the apex and aortic area. (Table 3.)

TABLE II

Location of Murmurs

Intensity	Pulmonic	Apical	Aortic	Total
1 minus	2	1	0	3
1	9	4	4	17
1 plus	14	8	0	22
2	7	1	0	8
2 plus	6	2	0	8
Total	38	16	4	58

TABLE III

Location and Intensity of Combined Murmurs

No. Patients	Pulmonic	Apical	Aortic
4	2	1	–
2	1	1+	–
1	1+	1+	–
1	1	1	–
1	2	–	1
1	2	–	1
1	1	–	1

None of the murmurs was louder than 2 plus in intensity. In 16 individuals the intensity ranged from 2 to 2 plus, whereas in 31 the intensity ranged from 1 minus to 1 plus. In 27 patients the murmurs over the pulmonary orifice ranged from 1 plus to 2 plus and in 11 instances murmurs of the same range of intensity were present over the apical region. It is evident then, that not only was the greater number of murmurs heard over the pulmonary region, but that in this region they were of the greatest intensity.

Twenty-six observations were made in 20 patients with fever either artificially produced by intravenous typhoid vaccine or malaria during the course of treatment or as a result of illness. In only four were transient systolic murmurs produced during the height of fever. The average temperature of these patients was 104.4° F., while the average temperature of those in whom no murmurs appeared was 103.4° F. There were no substantial differences in the pulse rate or blood pressure readings in the patients who developed murmurs and those who did not.

Although there are other factors involved, it follows that fever alone can occasionally account for slight transient systolic murmurs.

The effect of anemia on the development of the systolic murmur was studied in a small group of cases. In three patients a systolic murmur was present during anemia, which disappeared when the blood returned to a higher level. The average hemoglobin in these three cases was 43 per cent and the average red blood cell count was 2.5 million. The corresponding determinations, when the murmur had disappeared, were 70 per cent and 4.1

million. In one of these instances the murmur was of grade 2 plus intensity at the pulmonary and apical regions and in the other two the intensity was of grade 1 plus. There were three cases in which no murmurs were heard during a moderate degree of anemia, when the average hemoglobin was 54 per cent and the red blood cell count was 2.3 million. From this it seems that the relationship between anemia and a systolic murmur is inconstant. There can be no doubt, however, that in some cases anemia, of itself, can account for the presence of a systolic murmur.

A great many investigators believe that transient systolic murmurs are dependent upon the increase in blood velocity,[1, 2, 4] inasmuch as the conditions in which they appear have been shown to have an increased velocity of blood flow.[10] Fahr [4] has applied this principle in an interesting manner and an explanation may be made on the basis of the critical velocity of blood flow. This factor has been defined as the velocity of flow in a vessel with parallel walls beyond which the flow is no longer steady and becomes turbulent. Any considerable increase in velocity, therefore, determines turbulent flow. Should the velocity of blood flow increase decidedly, one might expect the appearance of murmurs. Since the greatest velocity is produced during systole, these murmurs should be largely systolic.

Determinations of the rate of blood flow have been made in some of the conditions associated with a systolic murmur, such as hyperthyroidism and anemia, and found to be increased. There are other states, however, notably neuro-circulatory asthenia, associated with a faint systolic murmur and a normal rate of blood flow. Such hearts often have hypertonic sounds, as if the ejection of blood from the heart is snapping, as occurs in hyperthyroidism, and it is conceivable that the flow from the heart through the great vessels is increased in rate, although measuring the speed of blood through the entire circuit gives normal figures.

It has been shown that nitrites increase the cardiac output.[11] In addition animal experiments [12] have demonstrated that nitrites produce a rise in pulmonary arterial pressure as a result of greater minute output associated with cardiac acceleration and increased venous return, and that their effect upon pulmonary vessels is the same as on the systemic vessels, though less marked.

Another group favors the relative changes between the heart and great vessels as the most probable causative factor.[2, 4, 13] In such circumstances a relative stenosis as represented by a more or less rigid pulmonary or aortic ring, associated with dilatation of the vessel beyond, would be conducive to the appearance of a systolic murmur at the base. It has been shown that amyl nitrite produces a decrease in the size of the heart shadow in animals [14] and in humans the drug has also produced a decrease in the transverse diameter of the heart and an increase in the aortic shadow, in which the pulmonary vessels probably play a part.[15] Since the walls of the pulmonary artery are generally more distensible than those of the aorta, a relative stenosis is likely to be more marked at the pulmonary orifice, thus resulting in systolic murmurs at this area more frequently. The fact, that in this

series of cases given amyl nitrite the systolic murmurs were most frequently heard when the pulse rate had begun to drop and the blood pressure had risen above the initial level, seems to support the increased velocity of blood flow as a plausible explanation. It is possible that a relative stenosis may well be involved in this mechanism, also.

Furthermore, it should be mentioned that in the conditions investigated in this study no systolic murmurs of grade 3 intensity or greater were detected. This, we feel, is strong evidence in favor of the association of the louder murmurs with organic cardiovascular lesions.

Conclusions

1. Observations were made in 100 individuals, showing no evidence of heart disease, on the effect of amyl nitrite in the production of murmurs. In 47 individuals a systolic murmur developed. In none did a diastolic murmur or a systolic murmur of grade 3 intensity or greater occur. Murmurs of grade 1 intensity were about twice as common as grade 2 and they were more common at the pulmonary region than at the apex.

2. The systolic murmur that develops following amyl nitrite was found not to be due to the increased pulse rate but was found to be present as the rate began to slow.

3. Twenty-six observations in 20 patients were made on the effect of fever. In only four were systolic murmurs detected.

4. Observations in a small group of cases with anemia indicate that the relationship between anemia and the development of the systolic murmur is inconstant. There are some cases, however, in which the presence of the former, of itself, can account for the latter.

5. In the production of systolic murmurs a factor, that we regard as of some importance, is the velocity with which the blood is ejected from the heart. In many of the conditions (apart from organic heart disease) in which systolic murmurs are present, the velocity of blood flow is increased.

6. The fact that systolic murmurs of grade 3 or greater were not detected in the conditions that were investigated in this study, is further evidence that these louder murmurs are probably associated with organic cardiovascular disease.

The authors wish to express their appreciation to Dr. S. A. Levine for his many helpful suggestions and valuable criticism.

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THE DUAL NATURE OF THE ACTION OF INSULIN UPON THE HEART *

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IN a previous communication [1] it was shown that the characteristic electrocardiographic changes resulting from insulin hypoglycemia could be obtained in elderly diabetic patients with cardiovascular disease, by the use of therapeutic doses of insulin in amounts which did not cause hypoglycemia. Since similar results could be obtained in these patients by the use of low carbohydrate diets without insulin, and since in both insulin hypoglycemia and in our therapeutic experiments the insulin effects tended to be reversed upon the administration of carbohydrate, it seemed probable that the electrocardiographic distortions were secondary to the effects of the insulin on the available carbohydrate supply rather than to a primary action of the insulin upon the myocardium. Our results, however, did not preclude the possibility that some of the deleterious effects of insulin might not be reversed by the administration of carbohydrate. This latter possibility led us to the present investigation on animals, in which a more rigorous separation of the two factors was possible.

Our first approach to the problem was to observe the effects of the administration of adequate doses of carbohydrate in animals which had received large doses of insulin. The carbohydrate was administered either before or after hypoglycemia had occurred. The results of these experiments made it desirable to study animals in which hypoglycemia was produced without hyperinsulinemia. For this purpose evisceration was employed.

METHODS

In the insulin experiments, our method was, in brief, to produce marked hyperinsulinemia at varying blood sugar levels. A dog was trained to lie quietly on his right side throughout the whole experiment. At the beginning of each experiment, electrodes, consisting of copper wire wound around flannel bandage soaked in concentrated salt solution, were applied to the shaven limbs. At appropriate times blood was obtained by venous puncture from the external saphenous vein and the blood sugar content determined by the Somogyi modification of the Shaffer-Hartman method.[2]

In the evisceration experiments hypoglycemia was obtained by removing the source from which the blood derives its sugar content.[3] Complete evisceration was performed in preference to hepatectomy in order to remove the

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possibility of inadvertent hyperinsulinemia. Complete eviscerations were performed both by the well-known two-stage method or by a modification of the newer one-stage method of hepatectomy described by Markowitz et al.[4] The animals were fasted for 24 to 48 hours before evisceration. Both the operations and the experiments were carried out under barbital anesthesia. Electrocardiograms and blood sugar estimations were done as in the previous experiments, but since the animals were anesthetized it was found more convenient to use German silver electrodes inserted subcutaneously. Blood samples were obtained from a cannulated artery. In a few experiments blood lactic acid was also determined. Mean arterial blood pressure was continuously recorded on a smoked drum from one carotid artery.

Following the completion of the evisceration, simultaneous electrocardiograms and samples of blood for sugar analyses were taken at 20 minute intervals. The first few blood sugar determinations were made as quickly as possible. By plotting these values and projecting the curve, a rough estimate of the time at which the animal would enter an adequate hypoglycemic state could be made. When, from this calculation, it was thought that the animal's blood sugar level had reached a point below 20 mg. per cent, ¼ to ½ gram dextrose per kg. body weight was administered intravenously. The animal was then observed during a second and sometimes a third such period.

The possible effect of volume and fluid administration in the injection of dextrose was controlled in several experiments by the administration of equivalent amounts of isotonic saline.

Results

The electrocardiographic changes which we observed during insulin hypoglycemia were similar to those obtained by others and by ourselves in previous work. (Cf. figure 1.) It may be seen that while glucose administration may completely reverse the insulin effects on the electrocardiogram (exp. 2, table 1) this is by no means a constant result. Furthermore, the degree of electrocardiographic distortion bears no constant relationship to the coincident blood sugar level (exps. 3 and 4, table 1). These observations are also apparent in experiments 5 and 6 (table 1) where insulin was given with the glucose, after hypoglycemia had developed. In experiment 7 (table 1) the electrocardiographic distortion occurred following the administration of insulin, in spite of the simultaneous and repeated administration of sufficient glucose to prevent hypoglycemia. It is interesting to note that the electrocardiographic distortion in this experiment was greater at the higher blood sugar level than at the lower.

These experiments indicate that insulin hypoglycemia is accompanied by electrocardiographic changes which may be only partially reversed by sugar administration and which bear no constant relationship to the blood sugar level. The dual nature of this insulin effect led us to attempt to determine the effects of hypoglycemia not due to insulin.

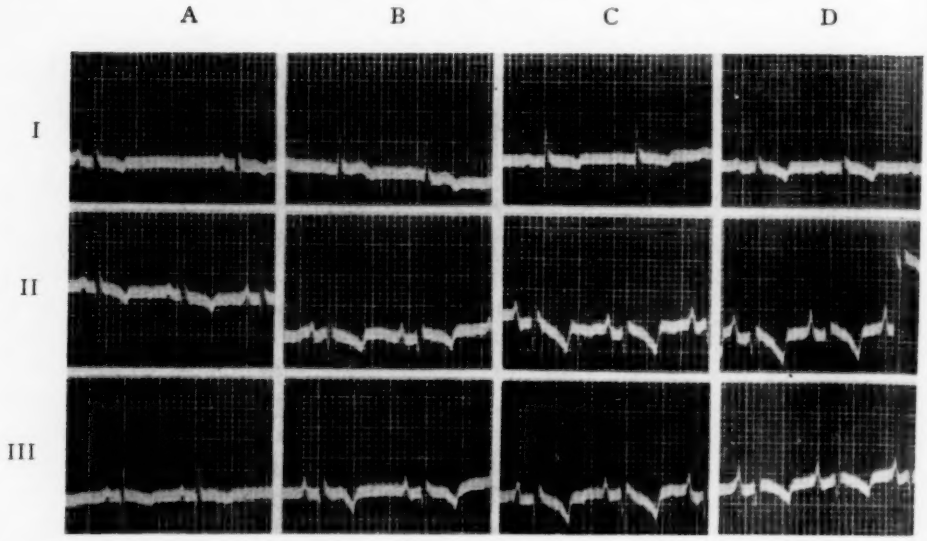

FIG. 1. Electrocardiograms (experiment 4, table 1) showing the characteristic insulin effect on the T-wave. Segment A is the control, segments B and C show the progressive change. Segment D shows the persistence of this change following the elevation of the blood sugar by sugar administration.

In the evisceration experiments we observed changes in the electrocardiograms accompanying hypoglycemia, which were reversible upon the administration of dextrose.

Hypoglycemia caused a decrease in the amplitude of the upright T-wave, in all leads. (Our series contained no instance of an initially inverted T-wave.) In two cases the upright T-wave actually became inverted during hypoglycemia; in one instance this occurred in Lead I, in the other case (figure 2) it was seen in all leads. In one animal the control electrocardiographic records after operation showed inversion of the QRS complex in Leads II and III. Hypoglycemia in this case increased the amplitude of the upright T-wave in these leads.* In every case, the above changes persisted and progressed with the hypoglycemia, and the changes in the T-wave disappeared only upon the elevation of the blood sugar level by the administration of sugar. As illustrated in table 2, the magnitude of the changes due to hypoglycemia could not be strictly related to the degree of hypoglycemia which occurred. However, with two exceptions, no change was seen until the blood sugar fell below 30 mg. per cent.

In addition to the hypoglycemia effects we also observed progressive changes in the electrocardiogram which bore no relationship to the glycemic level. These latter changes which were apparently related to the functional state of the circulatory system, progressed steadily, with the hypoglycemia effects superimposed upon them. Characteristic electrocardiographic

* This change in the T-wave is opposite in direction to that obtained in the other experiments, and is related to the reversed direction of the QRS complex. This confirms the conclusions drawn from similar observations in our previous work.[1]

TABLE I

Insulin Experiments

Exp. No.	Time	Material Administered	T-Wave Distortion *	Blood Sugar Level	Remarks
	Min.			Mg. %	
1	0		0	92	"Control" experiment. Insulin effect marked and progressive for 4 hours.
	10	15 units insulin †			
	130		+++	17	
	190		++++	15	
	250		++++	11	
2	0		0	80	Insulin effect completely reversed by sugar.
	10	16 units insulin			
	110		+++	22	
	120	13 gm. glucose †			
	175		0	72	
3	0		0	84	Insulin effect partially reversed by sugar, in spite of slight elevation in blood sugar level.
	10	17 units insulin			
	125		++++	20	
	150	13 gm. glucose			
	190		++	26	
4	0		0	87	Insulin effect obtained at relatively high blood sugar level, and not reversed in spite of marked increase in blood sugar level.
	10	15 units insulin			
	70		++	57	
	130		+++	42	
	145	10 gm. glucose			
	170		+++	131	
5	0		0	82	Insulin effect only partially reversed by large amount of sugar when insulin given with latter.
	10	15 units insulin			
	130		+++	13	
	155	25 gm. glucose			
		15 units insulin			
	210		++	146	
6	0		0	72	Insulin effect only partially reversed by large amount of sugar when insulin given with latter.
	10	16 units insulin			
	130		++++	15	
	140	25 gm. glucose			
		10 units insulin			
	190		+++	115	
7	0		0	80	Insulin effect not prevented by simultaneous and continued sugar administration.
	10	20 gm. glucose			
		15 units insulin			
	70	8 gm. glucose			
	115		++	94	
	130	8 gm. glucose			
	230		+	40	

* The electrocardiographic T-wave changes are recorded in arbitrary units to indicate in a semi-quantitative manner the relative amount of change observed by comparing the entire series of records. Figure 1 depicts typical electrocardiographic changes of degrees ++ and +++. 0 indicates the control contour.

† Insulin given subcutaneously, glucose intravenously.

TABLE II

Evisceration Experiments *

Exp. No.	Blood Sugar Level	Blood Pressure	T-Wave Distortion
	mg. %	mm. Hg	
1	215	90	0
	59	65	0
	413	65	0
2	242	62	0
	125	63	0
	350	63	0
3	87	77	0
	trace	58	+
	65	55	0
	4	55	+
	108	58	0
4 †	53	160	0
	15	38	++
	92	75	0
5	98	85	0
	11	70	+
	83	85	0
	9	70	+
6 ‡	49	170	0
	26	167	++
	9	115	++++
	157	120	0
	13	60	+
	237	80	0
7	115	180	0
	74	125	0
	173	120	0
	94	115	+
	222	90	0
8	75	135	0
	28	50	+
	109	45	0
	22	50	+
9 §	52	125	0
	15	80	++
	153	100	0
	11	75	+
	248	78	0
10 ‖	77	120	0
	22	23	+++
	178	20	0
	37	18	+
11	45	150	0
	8	125	+
	53	140	0
	19	135	+
	177	115	0

* Summary table of approximately the highest and lowest points of the experiments as regards the blood sugar level. The values in each experiment are given in chronological sequence. Rough quantitation of the T-wave changes as in table 1. Figure 2 depicts typical T-wave changes of degrees ++ and ++++. 0 indicates the control contour.

† QRS diphasic in Lead II, inverted in Lead III.

‡ Direction of T-wave reversed.

§ QRS inverted in Leads II and III.

‖ Direction of T-wave reversed in Lead I.

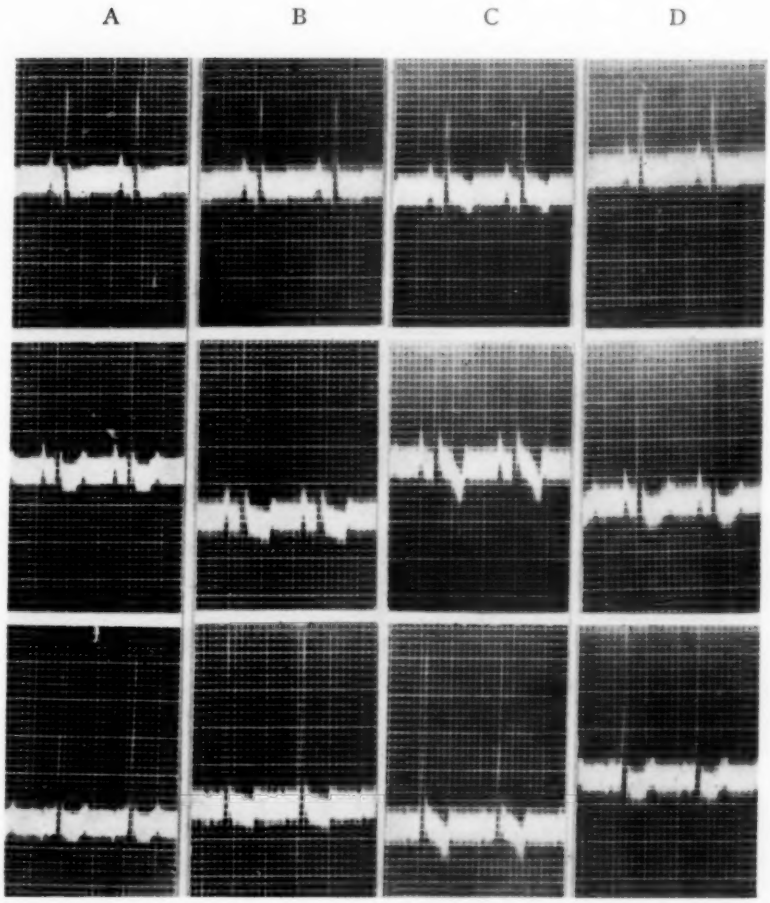

FIG. 2. Electrocardiograms (experiment 6, table 2) showing reversal in direction of the T-wave in all three leads during hypoglycemia produced by evisceration. Segments A, B and C are records taken at increasing intervals after the evisceration, at blood sugar levels of 49, 26, and 9 mg. per cent respectively. Segment D is a record taken after the administration of dextrose, when the blood sugar level was 157 mg. per cent. This shows the completely reversible nature of the T-wave change caused by hypoglycemia without hyperinsulinemia.

changes, unrelated to the glycemic level, also appeared when the blood pressure fell to extremely low levels. In such instances, an increase in blood pressure brought about by the injection of isotonic saline, returned the electrocardiogram toward normal. However, saline repeatedly failed to affect the electrocardiographic changes accompanying hypoglycemia, which were reversed by the injection of sugar.

These results demonstrate beyond doubt that hypoglycemia per se affects the electrocardiogram.*

*At the suggestion of Dr. A. B. Luckhardt we attempted to observe the effects upon the electrocardiogram of chronic hypoglycemia caused by continued phlorhidzin administration. We found, however, that phlorhidzin produces electrocardiographic changes which differ from those produced by insulin and which, furthermore, are not reversible by raising the glycemic level.

Summary and Conclusion

1. Insulin hypoglycemia is accompanied by electrocardiographic changes which are only partially reversible by the administration of sugar. In addition to its hypoglycemic effects, insulin has been shown to affect the electrocardiogram through some other mechanism.

2. It has been shown that hypoglycemia without hyperinsulinemia produces electrocardiographic variations which are completely reversible by the administration of sugar.

3. Our present results indicate that some of the electrocardiographic changes obtained in our previous studies upon elderly diabetic patients with cardiovascular disease,[1] must have been due to that action of insulin which is not reversed by carbohydrate. In the light of our previous work it may therefore be concluded that the deleterious action of insulin on the heart, associated with the electrocardiographic changes, probably cannot be completely antidoted by adjusting the carbohydrate intake. This does not vitiate our previous conclusions as to the importance of an adequate carbohydrate supply to counteract the harmful effects of relative or absolute hypoglycemia. It does, however, direct attention to the necessity for further study of the significance and extent of the possible harm which may result from that action of insulin which is not related to the hypoglycemia.

We are indebted to the Department of Chemistry for assistance with chemical determinations.

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A CRITICAL REVIEW AND EVALUATION OF TESTS FOR LIVER FUNCTION *

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The functions of the liver have been shown by Mann [1] and his coworkers to vary more or less independently of one another, and disturbances or cessation of one function may be coincident with normality in the other. Therefore, it is necessary to have an understanding of the various functions of the liver before a clear conception of the different tests for liver function can be discussed.

In order fully to understand the various functions of the liver certain anatomical, physiological and chemical aspects of this organ must be considered.

It is a well known fact [2] that the liver has great power of regeneration, and even in a case where liver damage clinically seems very evident, enough regenerated tissue may have formed to make functional tests appear as though the liver were normal. A large amount of structural change may be present in the liver before a functional disorder is evident, and on the contrary a very marked derangement of function may be present without any structural change in the liver. However, when symptoms of liver diseases are very marked there is usually some structural change that can be observed.

The liver is thought to be more or less concerned with the following functions:

1. The secretion and excretion of bile.
2. The destruction of red blood cells.
3. The coagulation of the blood.
4. The storing of fat taken from the food to be set free as required.
5. The metabolism of proteins and the formation of urea.
6. The formation of glycogen from ingested carbohydrates and proteins; reconversion of glycogen into glucose as required for the nutrition of the body.
7. The protective function of detoxicating poisons brought to it from the gastrointestinal tract and other parts of the body; and the removal of foreign substances from the blood.
8. The rôle played in concentration and dilution of the blood plasma in heat regulation.

It is not within our province to enter into a discussion of all the physiological facts concerned with these functions, and we refer to recent text-

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books and articles on the advance in physiology in the past few years for details.

Over a period of years, methods have been devised to test most of these separate functions of the liver, but none has been advanced that will evaluate these functions as a whole, so it is necessary to study each function separately.

In certain instances most of these functions have been tested at about the same time to determine the relationship of each, in the hope that some composite test may be devised to give us a better understanding of liver function as a whole.

Since we [3] started the study of liver function in 1925, an attempt has been made to gather some data on patients studied with all the known tests. So far no definite conclusions can be drawn, but it is hoped to publish definite data in the near future which may throw some light on this rather indefinite subject.

Some tests act as a test for several functions, and it is hard to classify each under its separate function. Many writers [4] in the past few years have given a very clear conception of the various tests in their reviews, by grouping the tests under functional heads.

The Secretion and Excretion of the Bile

It is possible to study the activity of the secretion of the bile by: (1) a study of hepatic products in the stool and urine; (2) a study of the duodenal contents by drainage, and (3) a study of the rate of disappearance from the blood stream of substances specifically secreted by the liver.

Inasmuch as disease of the gall-bladder is often associated with chronic inflammation of the liver and of the biliary passages, one must consider this organ as a factor in the picture of liver disease and determine if it is involved in the process. However, in most cases of cholecystitis the changes produced have very little effect on the functional efficiency of the liver.

Although not considered as strictly a test for liver function, the method of cholecystography as introduced by Graham and Cole in 1924, has been of great help in differentiating gall-bladder from liver disease.

The intravenous injection of thorium dioxide, followed by roentgen-ray pictures of the liver, has been used by Yater and Otell,[5] to demonstrate cancer, cirrhosis, cysts and abscesses of the liver. Very definite pictures, useful in differential diagnosis, of these conditions can be obtained by this method.

Likewise, the study of the duodenal contents by Lyon's [6] drainage method, as suggested by Meltzer,[7] is very helpful in the study of infections of the gall-bladder, biliary tract and liver, as well as to determine if jaundice is caused by obstruction of the common bile duct or due to other causes. The microscopic study of bile obtained by duodenal drainage is important, as it may reveal evidence of definite infection, or of crystals of cholesterol or calcium bilirubinate, which are important in the diagnosis of cholecystic disease.

All are familiar with the value of the well known tests for bile pigment in the urine, with the associated absence of bile pigments in the stools, in determining obstructions of the biliary flow.

The view of Aschoff [8] that bilirubin is developed in the reticulo-endothelial system, from the destruction of red blood cells, is supported by McNee [9] and others. Cells of this system are found in the spleen, bone marrow, lymph glands and interstitial cells of the testis, and the Küpffer cells of the liver. The bilirubin thus formed is passed through the polygonal cells of the bile capillaries, and after passing into the bile passages is oxidized into biliverdin. The bile pigment thus passes into the intestinal tract and, as shown by Wallace and Diamond [10] and others, is converted into urobilin and urobilinogen. That part of the urobilin which is not excreted with the feces as stercobilin, is reabsorbed into the portal circulation and carried back to the liver where it is reconverted into bilirubin.

From this it can be readily seen that if there is parenchymal liver damage, the urobilinogen will not be taken up by the liver, but will be shunted into the general circulation. Due to the fact that the kidney threshold for urobilinogen is very low, it is rapidly excreted in the urine. When complete obstruction of the biliary flow is present, no bilirubin as biliverdin can enter the intestinal tract, and consequently no urobilin can be formed. In non-obstructive diseases of the liver in which there is parenchymal damage, the bilirubin finds its way into the blood stream by the liver cells and appears in the urine in increased amounts.

From the foregoing, the importance of an estimation of the bilirubin, urobilin and urobilinogen in the urine, as well as of bilirubin in the serum becomes evident.

Icterus Index. The amount of bilirubin in the plasma is determined by the icterus index. The simplest method is that described by Mullengracht and modified by Maue:

"Approximately 5 c.c. of blood is withdrawn from a vein into a clean, dry test tube. The serum is carefully pipetted off, and a comparison of color is made in a colorimeter, against a standard 1 to 10,000 solution of potassium bichromate. The standard is set at 15 mm. and this number divided by the number on the serum scale, represents the icterus index. If the serum is highly colored, suitable dilutions must be made before reading. The icterus index for normal sera falls between 4 and 6, and in most cases ranges around 5. The point at which visible jaundice appears varies considerably in different cases, but generally is around 15."

"There exists then, a zone of bilirubin retention that can be detected by this test, though no visible jaundice is present." The progress of the jaundice either upwards or downwards may be followed by this method.

However, in chronic liver disease, the icterus index is of little value, except to follow the course of the disease and to detect the early onset of jaundice.

The Van den Bergh Test. By means of the Van den Bergh test it is

possible to determine if the bilirubin present in the blood serum has passed through the polygonal cells into the bile and been shunted back into the blood stream, because of obstruction to the bile passages. Under these circumstances the test yields the so-called "direct reaction." If the bilirubin present is due to the breakdown of hemoglobin, and has not passed through the polygonal cells of the liver, and possibly only through the Küpffer cells, the reaction is "indirect."

To perform this test, a solution "A" is made from 1 c.c. of sulphanilic acid, 15 c.c. concentrated HCl and 1000 c.c. of distilled water. Solution "B" consists of 0.5 gram of sodium nitrite and 100 c.c. of distilled water. Immediately before use, 25 c.c. of solution "A" and 0.75 c.c. of solution "B" are mixed.

The blood is allowed to clot and the serum used.

Direct Reaction. One c.c. of serum and 1 c.c. of the mixed reagent are mixed. A bluish-violet color, which develops in from 10 to 30 seconds, is called a direct reaction. A small flake of caffeine sodium salicylate will hasten the reaction.

Indirect Reaction. To 1 c.c. of serum 2 c.c. of 96 per cent alcohol are added, centrifuged, and 1 c.c. of the fluid is pipetted off.

To this is added 0.5 c.c. of the mixed reagent. If a violet-red color develops at once, an indirect reaction is present.

To be decisive, the color change in the direct reaction must come on in from 10 to 30 seconds. A delayed direct reaction appearing in from 1 to 15 minutes has the same significance as an indirect reaction. Biliverdin is formed only in the bile passages as the result of oxidation of bilirubin, and is not present in the blood stream and does not give a Van den Bergh reaction.

Both reactions may be present in the same case, giving a so-called "biphasic reaction," which is usually found in toxic or infectious jaundice. This may be accounted for by the fact that the bilirubin in the blood, due to obstruction of the bile ducts, gives a prompt direct reaction, while the bilirubin dammed up from poisoning of the liver, gives a delayed direct reaction. Also, in hemolytic jaundice the increased viscosity of the bile may result in blockage of the bile capillaries, and both forms of bilirubin will be present in the blood, giving rise to a biphasic reaction.

The amount of bilirubin in the blood serum may be quantitatively estimated. As Van den Bergh says, this is not a quantitative determination, but "an estimation," by using the indirect reaction as mentioned above. McNee [11] suggests the addition of 1 c.c. of saturated ammonium sulphate to the mixture, centrifugation and comparison with a standard solution made of cobaltous sulphate. The normal amount of bilirubin present in the blood serum by this method is from 0.2 to 1.0 mg. per 100 c.c. (0.4 to 2 units). Recent findings of Jacobi [12] et al. indicate that the plasma instead of the serum may be used with equal accuracy in determinations of bilirubin.

Trumper and Cantarow [13] state that in selected cases of slight liver damage, it is possible to recognize liver insufficiency by the method of Harrop and Barron, in which bilirubin is injected intravenously, 1 mg. per kilogram of body weight. In normal persons it should be excreted from the blood stream in two to four hours. If bilirubin is still present at the end of four hours, the power of the liver to excrete the pigment is impaired.

The Destruction of Red Blood Cells

As has already been shown, this function of the liver is shared by other organs of the body, through the reticulo-endothelial system. A test of this function is not one of true liver function, but rather of hemolytic jaundice. However, the indirect Van den Bergh reaction, as already mentioned, is really a test of this function.

Greene, Snell and Walters [14] state that " in uncomplicated cases of hemolytic jaundice, the pertinent laboratory data are anemia and microcytosis, the high reticulocyte count and the increased fragility of the erythrocytes. The concentration of serum bilirubin, and the icterus index, are increased to a moderate degree, the former rarely exceeding 10 mg. in each 100 c.c. The Van den Bergh reaction is persistently indirect. This association of clinical jaundice with an indirect Van den Bergh reaction is diagnostic of a hematogenous type of jaundice. The coagulation of the blood is not disturbed. There is no retention of bromsulphalein or phenoltetrachlorphthalein. Duodenal drainage usually discloses a free flow of bile, with an increased content of bilirubin. The urine contains large amounts of urobilin and urobilinogen, and bilirubin is absent."

The Coagulation of the Blood

It has been observed [15] both clinically and experimentally that the coagulation time may be increased in diseases of the liver.

Although we have for some years given calcium by mouth and vein in jaundiced cases, to prevent bleeding, even if the serum calcium was normal, in the hope that an excess would help in the process of coagulation, recent studies seem to show this procedure is of no avail. Gunther and Greenberg [16] have shown that there is no deficiency in diffusible calcium of the blood serum in jaundiced cases, and it is this diffusible calcium that is available for clotting. They conclude that factors other than calcium must be sought in order to explain the abnormal bleeding of jaundiced patients.

This further supports the theory, as advanced by Howell [17] and others, that the liver is the principal site of the formation of fibrinogen.

If the liver is damaged to any extent, the blood fibrinogen is decreased, clotting time of the blood is increased and hemorrhage is apt to occur. As liver damage is repaired, the normal characteristics of the blood are restored.

It can readily be seen that the determination of the coagulation time is a very important test of this function of the liver. The sedimentation test [18]

is very useful in conjunction with the coagulation test, in order to detect a hemorrhagic tendency in patients. If the sedimentation rate is slow, hemorrhage is not so apt to occur; but if in the absence of fever, the rate is high, hemorrhage is more apt to occur.

Fat Metabolism

Fats are brought to the liver for storage to be acted upon before they are utilized. It is generally believed, but not proved, that H_3PO_4 and nitrogenous bases are added to the fatty acids in the liver to form phospholipines, which are sent to the tissues.

Enzymes, which possess the power of hydrolizing fats, are widely distributed in the body and are known as lipases. Whipple [19] has shown that injury to the liver causes a rise of blood lipase and has devised a test to measure this abnormality.

Normally, in terms of tenth normal acid, the blood lipase should be from 20 to 30 c.c. in normal persons and is usually constant. In liver necrosis Whipple has shown the blood lipase rises from five to eight times the normal level. He found a distinct rise when liver necrosis is produced by eclampsia, toxic poisons, acute yellow atrophy, cholangitis and abscess of the liver. Cirrhosis of the liver usually shows a subnormal blood lipase. True eclampsia may be differentiated from the toxemias of pregnancy by this test, as the toxemias usually do not produce a marked liver damage.

The method used by Whipple [20] is as follows: "Four tubes are prepared, each containing 1 c.c. of plasma or serum diluted with 4 c.c. of distilled water and 0.3 c.c. of toluol to check bacterial activity. To two tubes is added 0.26 c.c. of ethyl butyrate, the other two tubes serving as controls. The tubes are shaken, corked and placed in an incubator at 38° C. for 18 to 24 hours. They are then cooled in ice water, three drops of azolitmin added and titrated in pairs to a neutral reaction, using 1/10 normal acid and alkali." The two control tubes usually show the blood alkalinity to be 0.10 c.c. of 1/10 normal acid. The butyrate tubes give the amount of acid production beyond the neutral point, and represent the total acid production or lipolytic activity. In normal blood it is usually from 0.20 to 0.30 c.c. and may be called the amount of lipase in the blood serum or plasma as the case may be.

Rowntree, Marshall and Chesney [21] have made a comprehensive study of blood lipase in a variety of liver conditions and do not find it of much help in the diagnosis of early hepatic disease. K. C. Paul [22] reviews many papers on this subject, but does not express his own opinion of this method. Personally we have not had enough experience with estimations of blood lipase to give an opinion as to its value.

Under the function of fat metabolism we must not forget that satisfactory fat absorption is dependent on an adequate supply of bile salts in the small intestine. Consequently, excessive amounts of fat, soap fat and free

fatty acid will be found in the feces in any condition causing obstruction of the bile passage and causing obstructive jaundice.

Protein Metabolism

The liver plays a very important part in normal protein metabolism. Urea is formed in the liver after the deaminization of amino-acids. Investigation of liver function, from the standpoint of protein metabolism, is chiefly concerned with the excess of ammonia or decrease of urea in the urine, also with the ratio of blood urea nitrogen to the total urinary nitrogen. Mann has shown, however, that 90 per cent of the liver must be damaged before this function is impaired. Due to the fact that these tests show changes only in far advanced hepatic disease, they are of serious prognostic significance, but of no value as early diagnostic aids.

Hemoclastic Crisis Test. If there is enough damage to the liver to cause the entrance of protein split products into the circulation, an anaphylactic reaction is produced which is evidenced by a leukopenia and other anaphylactic phenomena. Based on these facts, the hemoclastic crisis test of Widal has been advocated as a method of study of liver function.

This test consists of giving a patient, on a fasting stomach, 200 c.c. of milk and taking a white count before ingestion of the milk, and repeating the count afterwards at 20 minute intervals for an hour, or until the leukocytic count has reached its minimum value. According to Snyder,[23] the blood pressure may show a slight change or may decrease 10 to 20 millimeters, the coagulability of the blood increases, the refractive index of its serum decreases markedly, and at the end of 90 minutes these changes proceed in the opposite direction.

This test, as shown by Fetter [24] and many others, has very little value in the diagnosis of liver disease since other factors, besides liver damage, can cause a variation in the leukocyte count and in the other phenomena. We have come to the same conclusion after using it for a very short time.

Uric Acid. Mann [2] and his co-workers in their experiments on dogs have used the level of uric acid in the blood and urine as a hepatic function test. They show a very definite increase in uric acid in both blood and urine after removal of hepatic tissue. Mann thinks this is the most efficient of the liver function tests performed on dogs. This test has not been proved of value in humans, due to the fact that large injections of uric acid may cause lesions in the kidney.

Minot and Cutler [13] have shown that the guanidine of the blood is increased in patients with acute arsphenamine hepatitis, acute catarrhal jaundice, preëclamptic toxemia and eclampsia; but that there is no deviation from the normal blood guanidine in chronic liver diseases such as carcinoma, syphilitic hepatitis, alcoholic cirrhosis and obstructive jaundice.

Carbohydrate Metabolism

As is well known, the liver plays a very important rôle in carbohydrate metabolism. As early as 1874 Bock and Hoffman [25] found that the blood

sugar was diminished after the liver had been cut off from the circulation. In 1901 Strauss [26] first suggested the use of levulose for testing liver function. He found that about 80 per cent of patients with liver disease exhibit a diminished tolerance for levulose, as evidenced by appearance of this substance in the urine. However, 10 per cent of normal individuals react positively to the levulose test.

In 1906 Bauer [27] first suggested the use of galactose as a better test for this function. The repeated experiments and classic investigations of Mann and his co-workers [28] have done a great deal to establish the importance of this test for liver function. Shay [29] and his co-workers have formed the conclusion that galactose offers the best means of investigating the carbohydrate function of the liver. They do not consider it an adequate routine test for liver function, but because of its limitations think it is ideal as an aid in the differential diagnosis of jaundice, and offers a means of identifying early the group of toxic or infectious jaundice.

Galactose Tolerance Test. The test is as follows:

The patient is fasted for 12 hours; the patient voids and the specimen is examined for sugar. Forty grams of pure galactose are given by mouth to the patient, dissolved in 500 c.c. of water which may be flavored with lemon juice.

Urine is collected if possible every hour for five hours. Each specimen is examined qualitatively for sugar by Benedict's test, and the total amount voided is then tested quantitatively for sugar and the total amount of galactose secreted in the urine is calculated. As much water as desired is given during the test, but nothing else.

In diabetic persons the dextrose may be removed from the urine by fermentation with yeast, leaving only galactose. In normal persons with no disturbances of the carbohydrate function of the liver, about 3 grams of galactose may be excreted in five hours; any amount over this may indicate hepatic impairment. Jaundice accompanying acute diffuse damage of liver cells will give a high value. The carbohydrate function of the liver is impaired and allows the galactose to pass into the general circulation whence, due to the absence of a kidney threshold for galactose, it passes into the urine. In obstructive jaundice without liver damage and in hemolytic jaundice the readings are normal.

The Antitoxic and Protective Function of the Liver

The liver is known to possess a detoxifying function in protecting the body against various toxic substances, entering through the intestinal tract. Such substances as indol, salicylic acid, cinchophen, menthol, camphor, phenol, etc., are believed to be oxidized in the liver or conjugated into relatively nontoxic substances and eliminated in the bile and urine. Various methods, based on these facts, have been proposed for the estimation of liver function, but until of late none has proved to be of any clinical value.

Recently Lichtman [30] has reported a test based on the oxidation of cinchophen for estimating the function of hepatic cells and reports enough data on cases tested by his method to entitle it to serious consideration.

This test is based on the fact that after the ingestion of cinchophen a product of oxidation oxy-cinchophen [2-(ortho-hydroxy)-phenyl-quinoline-4 carboxylic acid] appears in the urine. In disease conditions of the liver a larger percentage of oxy-cinchophen is excreted in the urine than is found in normal subjects. This is probably due to the fact that oxy-cinchophen represents an intermediary product in the destruction of cinchophen. The power of further catabolism of oxy-cinchophen is lost by damaged liver cells, and as the disturbance of the function of the cells increases, larger amounts of the oxy-cinchophen are excreted in the urine.

Cinchophen Test. The test is performed by giving the patient 0.45 gram of cinchophen and then estimating for 24 hours the amount of oxy-cinchophen in accurately measured specimens of urine at two hour intervals during the day and in a night specimen. This is done by boiling 5 to 10 c.c. of each specimen and filtering, and then to 0.2 c.c. of each filtrate adding concentrated hydrochloric acid to make a volume of 5 c.c. The mixture is shaken and brought to a boil. When bile is present only 0.1 c.c. of urine may be sufficient. If a yellow color does not appear, 0.4, 0.6 or 0.8 c.c. respectively of urine is added to concentrated hydrochloric acid to make a final volume of 5 c.c. and similarly treated until such a reaction has taken place. These tubes are then compared with a set of standard tubes containing oxy-cinchophen. "The percentage of oxy-cinchophen determined colorimetrically represents the concentration of this substance in 0.1, 0.2, 0.4, 0.6 and 0.8 c.c. of urine, respectively, diluted to a final volume of 5 c.c. It must be multiplied by the respective dilutions, 50, 25, 12.5, 8.33 or 6.25 to obtain the percentage of oxy-cinchophen in the original urine." The total amount of oxy-cinchophen is then calculated for the entire urine voided for 24 hours.

Lichtman believes this test measures quantitatively the extent of damage or dysfunction of the cells of the liver, and depends on a metabolic function of the liver that is apparently first to be disturbed in hepatic disease.

From our limited number of cases tested by this method, we have been unable to form any definite conclusion. In far advanced liver disease the results are not very satisfactory; but as a whole, we believe it offers many possibilities for future study.

The Removal of Foreign Substance from the Blood

For many years it has been known that dyes are removed from the circulation and eliminated almost entirely by the liver. Various dyes as asorubin S, rose bengal, phenoltetraiodophthalein, phenoltetrachlorphthalein and bromsulphalein have been used as a basis for liver function tests.

Bromsulphalein Test. In our own studies [3] with dye as a liver function test, we have used bromsulphalein and the technic, with slight changes, as introduced by Rosenthal and White [31] almost exclusively.

The technic briefly is as follows: A 5 per cent solution of bromsulphalein on a basis of 2 mg. per kilo. of body weight is injected intravenously. At the end of 30 minutes blood is withdrawn from a vein on the opposite arm. After the blood has coagulated and is centrifuged, the serum is removed, placed in two small tubes and four drops of 5 per cent sodium hydroxide are added to one tube to bring out the color of the dye, and four drops of 2 per cent hydrochloric acid added to the other to clear the serum. The amount of dye present is estimated by direct comparison with a series of standards by placing the cleared serum in front of a standard tube and comparing with the colored alkalinized serum.

In our [3] original work by estimating the dye present in the serum 5, 15 and 30 minutes after injection of the dye we established a standard of 28, 15 and zero respectively. For this, 25 cases were used in which the liver was proved to be normal at operation or autopsy, and all cases not so proved were not used.

From the series of pathological cases studied, we concluded that in all cases of liver destruction, the percentage of dye retention increased with advance of the disease; while in the extra-hepatic diseases with obstruction, the retention was high when obstruction was present, and decreased with removal of the obstruction. Also, that in the more destructive diseases as cancer, cirrhosis, etc., the retention of the dye at the end of five and 15 minutes was somewhat higher than in cases of liver enlargement from obstruction of the mechanical or catarrhal type.

Since our original observations, we have used a dosage of 5 mg. of dye per kilogram of body weight in cases where very slight liver damage was evident. Dye retention has been thus demonstrated in cases of slight liver damage which would be negative with the earlier technic. Nevertheless, even by this method we have found some cases with definite liver destruction at autopsy or operation, that showed no dye retention.

We still believe and agree with Robertson, Swalm and Konzelmann,[32] who in their recent article state that dye retention will detect impairment of liver function as frequently as any other test, and that this test along with an icterus index determination, most frequently agrees with the clinical picture present.

Rosenthal,[33] who originally introduced bromsulphalein as a liver function test, still thinks that in chronic liver disease the dye test will be positive more often than the serum bilirubin; but that some cases of latent jaundice occur in which an increase of serum bilirubin is present without dye retention, so that both tests should be employed. He also states that experimental and clinical experience has shown that in no case, in the absence of liver disease, is there retention of dye; and that definite retention is almost certain evidence of liver damage.

Rose Bengal Test. Our experience with the rose bengal dye test is very limited. Delprat and Stowe [34] think it is the best of the dye liver function tests and easiest performed. Kerr [4] favors this test over bromsulphalein, as rose bengal is eliminated entirely through the liver while the former is partly excreted by the kidneys.

The test is performed by injecting 10 c.c. of a 10 per cent solution of rose bengal intravenously, and taking samples of blood after a period of two and eight minutes. Colorimeter comparisons are then made with the two minute specimen as a standard and the amount of dye estimated. In a normal functioning liver this test should show about 50 per cent less dye in the eight minute specimen than is found in the two minute specimen. Failure to remove this amount of dye is a sign of diminished liver function.

The Anhydrous Function of the Liver

It has been shown by Barbour [35] and Marshall that when the body temperature is raised by fever, a large amount of fluid is lost from the blood stream and stored in the liver. It is thought that this may be due to chemical changes in the liver. Some clues to this problem are found in the work of Hashimato and Pick [36] which showed an increase of nonprotein nitrogen in the liver, following anaphylaxis. Barbour and Marshall think glycolysis may be a factor. A water balance test has been suggested by foreign writers [37] to test this function of the liver. So far it has not been developed enough in this country to be of any proved clinical value.

Summary

While an attempt has been made briefly to give the physiological principles underlying the various tests for liver function, there appears to be no experimental proof of a physiological basis for some of them. However, most of the tests are of clinical value, inasmuch as they are an index of disease present in the liver, as proved clinically or by inspection of the liver at operation or autopsy.

In order to arrive at any definite conclusion, it is necessary to perform as many of the functional tests, herein described, as can be conveniently done. In certain chronic diseases of the liver, in which the remarkable ability of the liver to regenerate has a chance to exert itself, most of these tests will show no impairment. If each case is carefully studied by the above mentioned tests, a very good clinical picture of the liver for practical purposes is presented.

It is impossible to state which tests should be used in all cases of liver disease. In most cases it is necessary to perform the bromsulphalein test, the icterus index test, the Van den Bergh test, the galactose tolerance test, to determine the amount of bilirubin and urobilin in the urine, and to study the cells of the blood before any definite diagnosis of liver disease can be attempted. If further data are necessary, many of the other tests may serve as aids in diagnosis.

Conclusions

1. No liver function test has yet been developed to measure the functions of the liver as a whole.

2. The various tests of different functions must be performed in order to give an understanding as to the liver damage as a whole.

3. The regenerative power of the liver may cause a discrepancy in the results obtained by the various tests.

4. Recent experiments and studies have made liver function tests more accurate than they were a few years ago.

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POSTURAL HYPOTENSION WITH SYNCOPE

REPORT OF A CASE CURED WITH EPHEDRINE SULPHATE*

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THE diagnosis of postural hypotension, as first described by Bradbury and Eggleston,[1] is predicated upon the following phenomena: (1) syncopal attacks on change of posture with a drop of the systolic blood pressure to the shock levels; (2) anhidrosis; (3) increased distress during the heat of the summer months; (4) slow and unchanging pulse rate with marked variation in the blood pressure; (5) slight decrease in the basal metabolic rate; (6) signs of slight and indefinite changes in the central nervous system; (7) blood urea at the upper normal level. Other relevant signs or symptoms in one or more of Bradbury and Eggleston's three cases were: (1) greater excretion of urine during the night than during the day; (2) loss of sexual desire and impotency; (3) a false general appearance of youth in comparison to the true age; (4) pallor of the skin and mucous membranes; (5) secondary anemia.

This condition must be differentiated from toxic vertigo, states of exhaustion, the Adams-Stokes syndrome, intracranial lesions, epilepsy and vestibular disease.

Until the appearance of the report of Ghrist and Brown,[2] the condition was not amenable to treatment. Their second case was relieved by ephedrine. In this connection the following case is reported because of the splendid response to the drug and complete relief for the past two years.

The theories as to the etiology of postural hypotension are admirably discussed by Bradbury and Eggleston [1] and Ghrist and Brown [2] and will not be gone into in this paper.

CASE REPORT

Mrs. H. M. S., an American farmer's wife, age 41, height 63 inches, weight 112 pounds, was referred by Dr. V. H. Mahan of New Lebanon, Ohio, on January 12, 1932 because of fainting spells and weakness. For the past 18 months she had been having attacks of syncope of increasing frequency and severity.[3] The least exertion precipitated an attack, especially if in the upright posture. Weakness was gradual in development. Her vision was failing. She observed that the recumbent posture, when an attack impended, would lessen the severity. During the past summer perspiration was much less than usual for her. Particularly annoying was the increased frequency of urination at night. She complained also of gastric distress, aching in the muscles, a growing lack of energy and ambition; while the family noted a tendency to moodiness and despondency.

Her father was living and well at 71. Her mother had died at 67 of meningitis. Her husband was well at 46. Five brothers and five sisters were living and well.

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From the Medical Service, St. Elizabeth Hospital, Dayton, Ohio.

She had six children living and well. Two miscarriages occurred, 18 and 20 years before.

The patient was a definitely undernourished woman, appearing younger than the stated age, though pale and anemic looking. The teeth were good. The tongue was slightly coated. The thyroid was not enlarged. She was hyposensitive by Libman's classification. An orthodiascopic tracing of the heart revealed the following measurements. Great vessels: 4.2 cm.; M.R. 3.8 cm.; M.L. 6.2 cm.; total 10 cm. Internal diameter of the thorax 23 cm. Cardio-thoracic ratio 43 per cent. No murmurs were present. The lungs were normal. The skin was dry and the tissue turgor less than normal. No pigmentation was present. The abdomen and genitalia were normal. The deep and superficial reflexes were normal. A gastrointestinal examination was normal. Electrocardiograms in the upright and recumbent postures showed only the change due to shift of the axis. The basal metabolic rate was minus 14 per cent. The Wassermann and Kahn tests were negative. The urine was normal. The hemoglobin was 68 per cent (Dare), red blood cells 3,600,000, white blood cells 7,900, polymorphonuclear leukocytes 74 per cent, small lymphocytes 24 per cent and large lymphocytes 2 per cent. The blood urea was 46 mg., blood sugar 90 mg., calcium 9 mg., and non-protein nitrogen 32.5 mg., in 100 cubic centimeters of blood. The blood pressure recumbent was 130 systolic and 84 diastolic, pulse 46; erect, it was 84 systolic and 60 diastolic, pulse 24.

The following special tests were done, after Bradbury and Eggleston, to check on the correctness of the diagnosis: Atropine, gr. 1/60 subcutaneously, produced no change in the pulse rate. Adrenalin, 1:1000 solution, 1 c.c. subcutaneously, elevated the pulse rate to 126 and caused nervousness and tremor. Pilocarpine, gr. 1/10 subcutaneously, induced marked sweating and salivation.

The patient had been given various endocrine preparations, epinephrine, strychnine, etc., without benefit, but when her true condition was recognized, she was advised to take 25 mg. of ephedrine sulphate every three hours (five doses per day). This dosage was continued for two weeks until January 26, 1932, when she was somewhat relieved, and then increased to 25 mg., each hour during the day. There then followed a remarkable improvement, and gradually the dose was lowered until in July 1932 it was discontinued and up to the present time none is needed. Her weight has increased from 112 to 156 pounds. The blood pressure phenomena are no longer present, she is able to do her own housework, the urinary symptoms have abated and the moodiness and despondency are relieved. At times she still complains of some general nervousness.

TABLE I

Effect of Posture on Urinary Output

January 12, 1932 In bed Amount voided	Time	January 16, 1932 Up and about Amount voided
125 c.c.	8 a.m.	20 c.c.
105	9	15
90	10	30
160	11	30
140	12 noon	10
110	1 p.m.	70
135	3	105
110	5	60
85	7	90
1060	Total day	430
380	Night	1290
1440	Day	1720

TABLE II

Effect on Blood Pressure and Pulse Rate of Posture without Muscular Work

Position	Time	Systolic blood pressure	Diastolic blood pressure	Pulse rate
	10:12	130	84	68
Horizontal	10:15	134	80	68
	10:20	84	64	24
Head up; 40 degree angle	10:24	80	58	65
	10:30	126	78	68
Return to horizontal	10:33	132	80	70
	10:36	172	108	64
Head down; 40 degree angle	10:39	169	106	68
	10:41	144	88	68
Returned to horizontal	10:45	140	84	70

SUMMARY

1. Postural hypotension with syncope is now a definitely recognized clinical entity.

2. Three cases have been reported by Bradbury and Eggleston,[1] two by Ghrist and Brown,[2] two by Vaughn,[4] one by Sanders,[5] one by Riecker and Upjohn [6] and the present case.

3. No therapy was found of value until Ghrist and Brown reported the successful use of ephedrine sulphate in their second case.

4. This is the second case benefited by the use of this drug and the change in the patient has been so marked that the word "cured" may be used advisedly in this instance.

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AN EVALUATION OF THE USE OF QUINIDINE SULPHATE IN PERSISTENT AURICULAR FIBRILLATION *

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SINCE the introduction of quinidine therapy as a treatment of auricular fibrillation by Frey [1] in 1918, enthusiasm for its use has gradually waned. As with many new products in medicine early reports were very favorable, but careful observation over a period of years has shown that the use of the drug in permanent auricular fibrillation is warranted only in exceptional cases. It is indeed questionable whether any form of therapy to restore the normal rhythm is indicated in this condition.

Time has shown that restoration of normal rhythm by quinidine is not apt to be permanent and it becomes evident that mere reversion to normal rhythm is no criterion of the value of the drug. What is of more importance is the consideration of those patients who, over a long period of time, have maintained a sinus rhythm following quinidine. Are these individuals better off than a well digitalized fibrillator in whom the ventricular rate is slow and who exhibits little if any pulse deficit? Is the benefit which results from restoration of normal rhythm sufficient to outweigh the dangers incident to the use of quinidine? In 1925, Levine and Wilmaers [2] concluded, both from a theoretical point of view and from a clinical study of 38 cases of auricular fibrillation treated with quinidine sulphate at the Peter Bent Brigham Hospital, that much of the enthusiasm for the drug was unwarranted.

The present study is of 49 additional cases of auricular fibrillation treated with quinidine sulphate at the Peter Bent Brigham Hospital within the past seven years. Of this group, 46 were classified as permanent fibrillators and three as transient. In 35, or 71.4 per cent, of these cases normal rhythm was restored. (Table 1.) Of 33 cases with adequate follow-up notes, only 17, or 51 per cent, remained regular over one year, and as far as is known only one patient has maintained a normal rhythm for three years and in that case hyperthyroidism was one of the etiological factors for the fibrillation. With few exceptions, patients were hospitalized and kept under careful observation. Attempts were made to choose cases that seemed most suitable for the treatment. All patients were thoroughly digitalized and quinidine given only when it was felt that the patient was at his maximum point of improvement. In some cases, however, quinidine was given as a last resort and the fatal outcome of one case was probably contributed to by this procedure.

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

TABLE I

Etiology	Made Regular	Regularity Maintained			Failures	% Made Regular
		under 1 yr.	over 1 yr.	unknown		
Rheumatic	15	7	8	0	10	60
Hypertensive and arteriosclerotic	2	1	1	0	2	50
Postoperative hyperthyroid	6	3	3	0	0	100
Rheumatic and hyperthyroid	4	2	2	0	0	100
Chronic myocarditis	5	1	3	1	2	71.4
No demonstrable heart disease	3	2	0	1	0	100
Total	35	16	17	2	14	71.4

Patients were given 0.2 gm. of quinidine sulphate by mouth as a test dose. On the following day 0.3 gm. was administered three times and each day the dose was increased 0.1 gm. until the rhythm became regular or until some toxic manifestation made further administration of the drug seem unwise. In this way patients received 0.4 gm., 0.5 gm., 0.6 gm., and 0.7 gm. three times a day on succeeding days. Occasionally it was necessary to go as high as 0.9 gm. three times a day. When regular rhythm was established the patient was placed on a maintenance dose of 0.2 gm. two or three times a day. Frequently it was necessary to increase the dose. One patient required a maintenance dose of 0.7 gm. three times a day.

SEX

The sex of the individual was of little importance. This is the consensus of opinion of most observers.[3, 4] In our series there were 27 males and 22 females. Of the former, 18 were restored to normal rhythm and of the latter, 17. There was apparently no relationship between sex and the duration of normal rhythm.

AGE

It has been pointed out by Weissman [5] that age is not an important factor in the successful restoration of normal rhythm by quinidine. In his series more than 80 per cent of the patients in whom sinus rhythm was established were 50 years of age or over. Wolff and White [4] state, however, that in their series, 80 per cent of the younger group whose ages ranged from 10 to 40 years were successfully treated, whereas in the older patients only 58.3 per cent were restored. They point out that age, so far as it has a bearing on the duration of heart disease, may be a factor of importance only in the cases of rheumatic disease with mitral stenosis. It was inferred that the duration of mitral obstruction might be directly related to the degree of auricular damage, the extent of which could hinder the restoration of normal rhythm. It must be remembered that auricular fibril-

lation is in most cases a late complication of heart disease and therefore a large percentage of the cases treated will be in older individuals.

In our series only 17 of the 49 cases were under 40 years of age. Of these 17 cases, 10, or 58.8 per cent, were converted to a sinus rhythm. Of the 32 in which the ages were over 40 years, 25, or 78.1 per cent, were restored. The duration of normal rhythm, however, on the average was longer in the younger than in the older group.

Etiology

Rheumatic heart disease, hyperthyroidism and hypertensive arteriosclerotic heart disease are the three chief etiological factors for auricular fibrillation. In almost 60 per cent of this series fibrillation was due to rheumatic valvular heart disease (table 1). Of the 29 cases so classified, 19, or 65 per cent, were restored to normal rhythm. All of the cases of hyperthyroidism when treated postoperatively responded to quinidine. In the non-valvular heart disease group, 63 per cent were converted to sinus rhythm. No heart disease was demonstrable in three cases and normal rhythm was established in all. Thus it would appear that the fibrillation due to rheumatic heart disease is less responsive to quinidine than are the other types. This is in agreement with the observations of Jamieson,[6] Clark-Kennedy,[7] Hay [8] and Viko, Marvin and White.[3]

Maynard [9] stated that in mitral stenosis the maintenance of sinus rhythm was not satisfactory due to the extensive pathology. It is questionable whether or not the pathological lesion itself plays any definite part in the duration of fibrillation or in the duration of normal rhythm following quinidine. Frothingham [10] in a pathological study of hearts of fibrillators and non-fibrillators found that there were no pathological changes common to all cases of auricular fibrillation. Nothing in his investigation indicated that the type of pathologic lesion found at autopsy could of itself be responsible for the onset and continuation of auricular fibrillation. Just as extensive lesions were to be found in both fibrillators and non-fibrillators.

Although all of the cases of hyperthyroidism treated with quinidine were converted to a sinus rhythm postoperatively in this study, only 66.6 per cent remained regular over six months. The resumption of auricular fibrillation in the minority of cases was probably due either to recurrent hyperthyroidism or some other form of independent cardiovascular disease.

Duration of Fibrillation

Duration of fibrillation is probably of some importance in quinidine therapy. One of the most difficult tasks facing the investigator of the problem of auricular fibrillation is that of obtaining an accurate history of the onset of the condition. In some individuals the sudden change in rhythm produces symptoms which when described are characteristic enough so that the onset may be accurately known. On the other hand, fibrillation

may exist for months and even years without the patient being aware of it. With these facts in mind, an approximation of the duration of fibrillation was made.

In table 2 it will be seen that the majority of patients had been fibrillating over six months. Of 19 fibrillating less than six months, 15, or 78 per cent, were restored to a normal rhythm; of 28 fibrillating over six months, 19, or 67.8 per cent, responded. Seven patients had a definite history of onset within a month before treatment was instituted. Of these, six were restored. Twenty patients had been fibrillating over one year and yet 15, or 75 per cent, were converted by quinidine. Thus we can draw no definite conclusions from these statistics as to the relative importance of duration of fibrillation to restoration of normal rhythm.

TABLE II

Duration of Fibrillation	Number	Made Regular	Duration of Regular Rhythm			
			under 6 mos.	6–12 mos.	over 1 yr.	unknown
Under 1 month	7	6	2	1	3	0
1–6 months	12	9	2	0	6	1
6–12 months	8	4	2	0	2	0
Over 1 year	20	15	6	3	5	1
Unknown	2	1	0	0	1	0

More important than mere restoration of normal rhythm is the duration of normal rhythm. According to Viko, Marvin and White,[3] in those patients in whom the duration of fibrillation was less than two months, not only was normal rhythm restored in a greater percentage, but it was also maintained to a much greater degree. They found, as was true in this study, that successful results could be obtained even though fibrillation had existed over 10 years. Our longest record of normal rhythm following quinidine was three years and this occurred in a patient who had been fibrillating for over two years. Thus it would appear that the duration of normal rhythm is not particularly influenced by the duration of fibrillation (table 2).

CLINICAL CONDITION OF THE PATIENT

The degree of congestive failure and the size of the heart have been considered decisive factors. Only one-fourth of those who had failure, but more than one-half of those who had not, maintained normal rhythm in the series reported by Viko, Marvin and White.[3] Better results have been observed in patients with little or no cardiac enlargement.[7, 8] Of the 35 cases restored in this series, 25 had moderate to marked cardiac enlargement, 19 had objective signs of decompensation and 16 had a palpable liver. (Tables 3 and 4.) Of the 14 in which quinidine failed, 13 had moderate to marked cardiac enlargement, only one being normal in size. Fifty per

cent of these failures showed signs of decompensation. Since all of the cases were thoroughly digitalized prior to giving quinidine, it did not seem that the clinical condition of the patient, per se, was an important factor in the restoration of normal rhythm.

TABLE III

Heart Size	X-Ray		Percussion	
	Made Regular	Failures	Made Regular	Failures
Not enlarged	4	0	6	1
Moderately enlarged	3	1	12	6
Markedly enlarged	8	4	2	2

TABLE IV

	Made Regular	Failures
Objective decompensation present	19	7
Objective decompensation absent	16	7
Palpable liver present	16	9
Palpable liver absent	19	5

No constant ratio was found between the size of the heart, the clinical condition of the patient and the amount of quinidine necessary to convert to a normal rhythm. One case showing moderate cardiac enlargement and objective signs of congestive failure on admission, who had been a known cardiac of nine years' duration with fibrillation for two and a half months, responded to 2.0 gm. of quinidine. Another patient whose onset of fibrillation occurred a few days before treatment was started and who showed no cardiac enlargement and but slight signs of decompensation, required 10.5 gm. of quinidine.

AURICULAR FIBRILLATION VS. NORMAL RHYTHM

In considering the use of quinidine in chronic auricular fibrillation it must be emphasized that the drug does not influence the natural progress of the underlying disease, nor is there any indisputable evidence that it tends to increase the life expectancy of the patient. What then is the advantage of a normal rhythm in a heart which has adjusted itself to a fibrillating condition and can be adequately controlled with digitalis?

It is a common conception that a heart that is fibrillating predisposes to circulatory embarrassment. Stroud, LaPlace and Reisinger [13] point out that " in terms of the physiology of the circulation it is really very questionable whether arrhythmia causes nearly as much circulatory embarrassment as one might, a priori, anticipate." It is indeed doubtful whether the well-digitalized, slowly fibrillating heart is not as efficient as the same heart converted to a normal rhythm. In the former condition the dangers incident to the use of quinidine are avoided.

Eyster and Swarthout [14] working on dogs showed that fibrillation diminished the cardiac output by 40 per cent. However, animal experimentation cannot be considered reliable in discussing such a strictly clinical manifestation as auricular fibrillation. Blumgart and Weiss [15] found that the circulation time in groups of patients with auricular fibrillation was prolonged from 75 per cent to 300 per cent. The prolongation was for the most part dependent upon the clinical condition of the patient at the time of the test. They stated that the prolongation of the circulation time was greater in proportion to the degree of decompensation than might be expected on the basis of determinations on similarly decompensated patients who showed a regular rhythm. The ideal test, however, would not consist of a comparison of similar cases but rather should be concerned with the improvement of circulation in the same individual following the production of a regular rhythm by quinidine. Certainly, the irregular rhythm at most plays only a small part in the prolongation of the circulation time and then only when the heart rate is in an uncontrolled state.

Lewis [16] emphasizes the fact that it is the uncontrolled state of the heart in exercise which constitutes the most serious feature of fibrillation. Blumgart,[17] studying the effect of exercise on the fibrillating heart, found that the rise of rate in fibrillators was approximately double that of normal subjects and that there was a delayed return to the normal resting level. Neither the exaggerated rise of the ventricular rate in response to exercise, nor the delayed return is due to the abnormal mechanism of impulse formation, for it is also exhibited by the same patients when the rhythm has been restored to normal.

In most of the cases sinus rhythm produced by quinidine is not permanent, and even if permanent generally requires the continued use of the drug. Thus the old idea that making the rhythm regular by quinidine frees the fibrillating patient from further drug treatment in contrast to the indefinite use of digitalis, is a fallacy.

Levine and Wilmaers [2] found that the return to a sinus rhythm following the use of quinidine produced no change in the vital capacity of the lungs. They pointed out that whereas a fibrillating heart that becomes embarrassed can be made to respond to digitalis, that same heart with normal rhythm becomes a difficult therapeutic problem in the face of decompensation. It is evident that there is no definite proof that the chronic fibrillating heart when adequately digitalized, so that the ventricular rate is slow and there is no pulse deficit, is less efficient than the heart restored to a sinus rhythm by the use of quinidine.

There is one condition in which obtaining a regular rhythm of the heart beat may be of distinct value. Those fibrillators whose chief complaint is a tumultuous beating of the heart even when adequately digitalized, are frequently strikingly improved when restored to normal rhythm. This is not invariably true and Stroud, LaPlace and Reisinger [13] state that the majority of their cases were no less " heart conscious " with restored sinus

rhythm than during the period of their fibrillation under effective digitalis therapy.

In the Cardiac Clinic at the Peter Bent Brigham Hospital, quinidine as a prophylactic measure has been used to prevent the onset of fibrillation. It is logically indicated in cases such as rheumatic heart disease with mitral stenosis where the development of frequent extrasystoles presages the onset of fibrillation. Small doses of quinidine sulphate often cause the disappearance of this irregularity and continued use of the drug may possibly be delaying the development of the inevitable state of fibrillation. It would also appear to be indicated in small doses in cases which will inevitably fibrillate even though there are no signs or symptoms suggesting that fibrillation is imminent.

Auricular Fibrillation and Auricular Thrombi

That auricular fibrillation predisposes to the formation of clots in the auricles has clinically been generally accepted. Lewis [16] found that in 76 autopsies on cases dying of chronic heart disease, in which thrombi were especially sought for, they were present in eight out of 23 in which fibrillation was present in the last illness and in only four out of 53 in which the mechanism had been normal. Harvey and Levine [18] in a study of mural thrombi found that in 31 cases of persistent auricular fibrillation, all but three had auricular thrombi (90 per cent). Of the other 80 cases in their series that showed thrombi but did not show auricular fibrillation only 43 had auricular thrombi (54 per cent).

Appreciating that fibrillators are in general older than non-fibrillators, the distinction between the effect of aging or duration of the disease and that of the arrhythmia itself in the production of thrombus formation has not been clearly made. An analysis was therefore made of 62 necropsy protocols of mitral stenosis cases at the Peter Bent Brigham Hospital covering a period of 15 years. From a statistical standpoint it was found that similar figures were obtained regardless as to whether the lesion was a pure mitral valve involvement or whether both mitral and aortic valves were diseased. There were 34 fibrillators and 28 non-fibrillators. Auricular thrombi were present in 20 of the fibrillators (58.8 per cent) and in only four of the non-fibrillators (15 per cent). They were present in the right auricle in eight cases, in the left auricle in six, and in both auricles in ten. Thrombi were most frequently found in those cases in which fibrillation had been present for over six months (table 5).

The average age of cases with auricular thrombi was from 10 to 15 years greater than those in which thrombi were not found. It must not be inferred from this that it is advantageous for these cardiacs to have mural thrombi, but rather that if they are fortunate enough to live longer, there is greater likelihood that mural thrombi will form. Of nine cases in whom the age was over 40 and fibrillation not present, four showed auricular

thrombi (average age 50 years). In the same age group in which fibrillation was present 12 out of 15 cases showed auricular thrombi (average age 49 years). This indicates that fibrillation apart from the aging factor is conducive to thrombus formation. That age, or possibly duration of the disease, is an additional factor is shown by the fact that there were no instances of thrombus formation in non-fibrillators under 40 years and only eight instances in 19 fibrillators in the younger group. Thus one must concede that the presence of fibrillation and the increasing years are both separate factors favoring auricular mural thrombosis.

It is Lewis' impression, however, that embolism due to detachment of the thrombi was not more common when the heart was fibrillating than when the action was normal. He feels that " while fibrillation predisposes to clotting, the normal auricular action favors the detachment of such clots." [16] Apparently the sudden onset of normal rhythm is an important factor in the production of emboli. MacKenzie [19] called attention to the fact that embolism occurs frequently when the rhythm spontaneously changes from fibrillation to normal. The not infrequent occurrence of embolism

TABLE V

Mitral Stenosis with Fibrillation

Case	Sex	Age	Duration of Fibrillation	Location of Thrombus	Other Valve Lesions
1	F.	23	7 years	No thrombus	None
2	F.	68	1 year	Lt. auricle	"
3	M.	21	(?)	No thrombus	"
4	F.	66	2 years	No thrombus	"
5	F.	31	(?)	No thrombus	"
6	F.	17	Recent	No thrombus	"
7	F.	55	4 years	Rt. auricle	"
8	F.	60	(?)	No thrombus	"
9	F.	42	3 years	Lt. auricle	"
10	M.	18	1 week	Rt. auricle	"
11	F.	43	5 years	Rt. auricle	"
12	F.	46	1 week	Rt. auricle	"
13	F.	40	(?)	Rt. auricle	"
14	F.	27	1 week	No thrombus	Aortic
15	F.	39	2 years	Rt. and lt. auricles	"
16	M.	16	1 week	No thrombus	"
17	F.	48	10 years (Par.)	Rt. and lt. auricles	"
18	F.	17	3 years	No thrombus	"
19	F.	27	1 year (Par.)	No thrombus	"
20	F.	18	6 days	No thrombus	"
21	F.	51	(?)	Rt. and lt. auricles	"
22	F.	32	7 years	Lt. auricle	"
23	F.	75	(?)	No thrombus	"
24	M.	45	3 years	Rt. and lt. auricles	"
25	M.	32	2 years	Rt. and lt. auricles	"
26	F.	17	Recent	No thrombus	"
27	M.	29	Several years	Rt. and lt. auricles	"
28	F.	39	1 year	Rt. and lt. auricles	"
29	F.	47	6 years	Rt. and lt. auricles	"
30	F.	36	3 years	Rt. auricle	"
31	M.	44	3–4 years	Lt. auricle	"
32	M.	22	(?)	No thrombus	"
33	M.	53	(?)	Rt. auricle	"
34	F.	45	14 months	Lt. auricle	"

TABLE V—*Continued*

Mitral Stenosis without Fibrillation

Case	Sex	Age	Duration of Fibrillation	Location of Thrombus	Other Valve Lesions
35	F.	55		No thrombus	None
36	M.	24		No thrombus	"
37	F.	14		No thrombus	"
38	F.	12		No thrombus	"
39	M.	40		No thrombus	"
40	M.	44		Lt. auricle	"
41	F.	52		No thrombus	"
42	M.	59		No thrombus	Aortic
43	M.	38		No thrombus	"
44	F.	58		No thrombus	"
45	F.	58		Rt. and lt. auricles	"
46	M.	58		Rt. and lt. auricles	"
47	M.	28		No thrombus	"
48	M.	26		No thrombus	"
49	F.	13		No thrombus	"
50	F.	19		No thrombus	"
51	F.	41		Rt. auricle	"
52	F.	16		No thrombus	"
53	F.	24		No thrombus	"
54	F.	15		No thrombus	"
55	M.	17		No thrombus	"
56	F.	13		No thrombus	"
57	M.	23		No thrombus	"
58	M.	40		No thrombus	"
59	M.	37		No thrombus	"
60	M.	14		No thrombus	"
61	M.	16		No thrombus	"
62	F.	59		No thrombus	"

Average age of patients with mitral stenosis with auricular fibrillation	37.0
Average age of patients with mitral stenosis without auricular fibrillation	32.6
Average age of patients with mitral stenosis with auricular fibrillation and with auricular thrombi	42.5
Average age of patients with mitral stenosis with auricular fibrillation and without auricular thrombi	31.2
Average age of patients with mitral stenosis without auricular fibrillation and with auricular thrombi	50.2
Average age of patients with mitral stenosis without auricular fibrillation and without auricular thrombi	29.6

at the time of, or at least soon after, the restoration of sinus rhythm tends to further support this point. When one considers that certain thrombi are exceedingly small and frequently tend to form in the extreme tips of the auricle, it will become obvious why the initial contractions of the auricle may fail to dislodge an embolus. The embolus may become dislodged a few months later from the constant auricular systole weakening the thrombus and eventually causing a part of it to become separated.

In 1923, Viko, Marvin and White [3] compared the frequency of embolism and other untoward results under quinidine in 484 reported cases of fibrillation with the frequency of embolism in 200 consecutive cases of auricular fibrillation at the Massachusetts General Hospital not receiving quinidine. During the short period of quinidine treatment in these 484 cases, embolism occurred in 15, or 3.1 per cent. In the 200 cases not treated with quinidine and presumably treated with digitalis, embolism occurred in 16, or 8.0 per

cent. They concluded that embolism is not much more frequent under quinidine treatment than under ordinary therapy. An analysis of these figures leads us to believe that the comparison is hardly valid. Embolic phenomena during quinidine administration usually occur at, or shortly after, the restoration of normal rhythm, or in exceptional cases before sinus rhythm is established. If emboli result from the use of quinidine they do so usually during the first 10 days of treatment. Thus in the 484 quinidine treated cases, the active therapy covered only some 4,840 days. The duration of treatment with digitalis is generally much longer, a reasonable average being one year per patient or about 70,000 days for the 200 cases. Certainly that drug which causes as many instances of embolism in 4,840 days as another in 70,000 days is the more dangerous. In fact the occasional embolism during long digitalis administration may be regarded as an inevitable accident of heart disease but when it occurs under quinidine therapy, in most instances, it is actually precipitated by that drug.

Untoward Effects

Various observers have reported innumerable types of toxic manifestations following the use of quinidine sulphate. With the exception of those cases in which normal rhythm is restored by small doses of the drug, symptoms of quinine intoxication are the rule. The most frequent of these are nausea, vomiting, epigastric distress, diarrhea, headache, palpitation, tinnitus, fever, mental depression, flushing, sweating, syncope and a feeling of apprehension. Skin manifestations including papular, scarlatiniform rashes, urticaria and inflammatory edema of the face have been reported. Symptoms such as transient attacks of failing or blurring of vision are occasionally encountered. Cerebral symptoms associated with diplopia and extreme excitability may result.[7]

The induction of heart failure has been reported several times.[20, 21] It is thought that this is due to the accelerated ventricular rate. The latter results both from vagal paresis and from the increased number of stimuli reaching the ventricle as the result of the slowing of the auricular rate. Carr and Spoenman,[22] adopting a rate of 130 as a limit calling for the withdrawal of quinidine, reported discontinuance of the drug for this reason in 11 cases out of 87 treated. The direct poisonous effect of quinidine upon the myocardium must also play some part in this effect.

Cases of sudden and temporary collapse with loss of consciousness and failure of respiration are occasionally encountered. Sudden death not embolic in nature has been frequently reported. Various explanations have been offered for this phenomenon including ventricular fibrillation, cardiac asystole due to failure of the S–A node to function when fibrillation ceases, heart block and marked vagal stimulation. White [23] suggests that the possibility of standstill of the whole heart due to depression by quinidine of the ventricular as well as the auricular pacemaker should also be considered.

Respiratory paralysis has also been reported. Schott [28] reproduced this quinidine effect in dogs and Gordon, Matton and Levine,[29] in cats. It is probable that this occurs more frequently in human cases than has been appreciated.

In this series of cases, three fatalities occurred during therapy. In two of the instances it was felt that the patients' death was an event that might have been postponed for a matter of years had they been treated with digitalis and had no attempt been made to regularize the rhythm. One was a 44 year old female with rheumatic heart disease and mitral stenosis. The onset of fibrillation occurred in this hospital 10 months before the patient's death. The use of quinidine one month after the onset of fibrillation successfully restored sinus rhythm. The patient showed little subjective improvement but continued with a normal rhythm until a few days before her last admission, when, despite a maintenance dose of 0.2 gm. of quinidine sulphate, twice daily, she reverted to the fibrillating state. At this time she had no objective or subjective cardiac decompensation. The heart was not enlarged and although fibrillating for the second time, the onset could certainly be considered as "recent." She was digitalized and quinidine was given in the routine manner. On the seventh day she received 0.8 gm. three times during the day but continued to fibrillate. Early the following morning she suddenly groaned and was dead. Necropsy revealed a thrombus in the left auricle but no evidence of emboli.

The second case was a 20 year old male with rheumatic mitral stenosis and insufficiency. The onset of fibrillation dated back about one and one-half years, shortly after which time he was restored to a sinus rhythm by the use of quinidine. He remained regular for one year and then reverted to fibrillation despite a maintenance dose of 0.2 gm. of quinidine daily. His rhythm was again made regular and remained so for about six months. With the last onset of fibrillation it was decided to attempt to obtain a regular rhythm with the patient ambulatory as his condition was quite good and there was no evidence of decompensation. Quinidine was administered in the usual manner. The day before his death the heart became regular, the last dose of quinidine administered being 0.8 gm. The following morning he arose and appeared to be feeling very well and his heart rhythm was regular. While resting that morning he suddenly gasped, became cyanotic and respirations ceased. No autopsy was obtained.

The other case might be considered as a poor risk. He was a 64 year old male with chronic myocarditis and fibrillation of approximately six months' duration. His heart was enlarged and on admission there was marked congestive failure with a liver palpable 4 cm. below the costal margin. Digitalis was administered but discontinued because of marked coupling of the pulse beat. Quinidine was then started and after having received 2.8 gm. in a period of 72 hours, the patient suddenly became dyspneic and unconscious. His heart was beating regularly and at a rate of 80 beats per minute. There was no motor paralysis. The attack was relieved by caffeine sodium

benzoate and examination one-half hour later showed a gross irregularity. Thirty minutes later the patient again became dyspneic and the heart beat exhibited a bizarre form of arrhythmia with varying periods of irregularity and regularity, occasionally slow and at other times fast. Suddenly no heart sounds were to be heard and after three minutes adrenalin was administered intracardiacly. The patient responded to such an extent that 30 minutes later the pulse was regular with a rate of 100. He had several more such attacks and although he responded for a while to stimulation, finally succumbed 80 hours after the onset of therapy. No autopsy was obtained.

It has been our experience at the Peter Bent Brigham Hospital that all cases of sudden death in which it seemed that quinidine was the cause have occurred in patients with mitral stenosis. This includes the two above-mentioned cases and three previously reported.[2] A review of the cases reported in the literature does not reveal this to be invariably so but it is true in the large majority of such cases. Thus we are inclined to agree with other investigators who consider long-standing valvular heart disease to be a contraindication to the use of quinidine.

Other various toxic phenomena occurred during the administration of quinidine. There were four instances of cerebral emboli, all recovering. One case of pulmonary infarction developed. Symptoms of cinchonism sufficient to require discontinuance of the drug occurred in eight cases and severe precordial pain resulted in three cases.

Quinidine Therapy in Fibrillation Due to Hyperthyroidism

In those patients in whom hyperthyroidism is the etiological factor for fibrillation, quinidine sulphate is an ideal drug after the hyperthyroidism has been cured and provided there is no other cardiac involvement of an organic nature. When there is in addition to the hyperthyroidism a rheumatic involvement of the heart, the etiological factor for the fibrillation is often the rheumatic lesion rather than the disturbance of thyroid function. The use of quinidine in an undamaged heart is probably a safe procedure; when myocardial or endocardial involvement is present, the same hazards discussed above obtain.

Quinidine should be administered only postoperatively and then only after a reasonable time has elapsed to permit spontaneous return to sinus rhythm. Two to three weeks is a sufficient test period, although shorter periods have been suggested. Anderson [11] believes that if auricular fibrillation recurs after quinidine has been administered postoperatively, residual or recurrent hyperthyroidism may always be suspected. In these cases one should also search carefully for some other etiological factor for the fibrillation. The addition of quinidine therapy following thyroidectomy when auricular fibrillation is present will restore normal cardiac rhythm in over 95 per cent of the cases. Hurxthal [12] states that if the hyperthyroidism is uncomplicated by cardiovascular disease, a return to normal rhythm may be anticipated in practically 100 per cent of the cases.

In all of the six cases of hyperthyroidism in our series treated postoperatively, and in four additional cases of hyperthyroidism complicated by rheumatic heart involvement and treated following subtotal thyroidectomy, a return to normal rhythm was obtained (table 1). Of the pure hyperthyroid cases three maintained normal rhythm over six months, two less than six months and no follow-up was available in one case. Of the four cases of rheumatic heart disease and hyperthyroidism, two remained regular over six months and two less than six months.

Indications and Contraindications

A consideration of cases regarded by investigators as unsuitable for quinidine therapy reveals that in chronic auricular fibrillation there remains only a small group in which the drug should be used. An idiosyncrasy to quinine and a previous history of embolism are universally agreed to be contraindications. Badly damaged hearts with long standing valvular disease, and more particularly if there is undoubted failure of compensation with venous engorgement, are considered unfavorable factors. The use of the drug is regarded as hazardous when there is severe myocardial damage even without decompensation. When angina pectoris has been relieved by the onset of fibrillation one should hesitate to convert the rhythm to normal and again subject the patient to anginal pain. Acute or subacute infective endocarditis, fibrillation with complete heart block, aortic disease, active hyperthyroidism, and the presence of chronic interstitial nephritis, all have been pointed out as contraindicating quinidine therapy.[8, 9, 12, 24, 25, 26, 27] Spiro and Newman [26] state, "it is almost useless to give a patient quinidine if he has auricular fibrillation and hypertension." Marked cardiac hypertrophy and long standing fibrillation are also considered unfavorable conditions. Some of these contraindications are obvious, but as to others one might readily take exception.

What then are the indications for the use of quinidine sulphate in chronic auricular fibrillation? One is forced to weigh the benefit derived by the patient as a result of making his heart rhythm regular against the danger incident to the use of the drug. There should be assurance that the patient will be objectively and subjectively in better health than if he were adequately digitalized and fibrillating with a slow ventricular rate.

Quinidine may be used with fair safety in cases in which the heart is normal. It is of distinct value in postoperative cases of hyperthyroidism uncomplicated by cardiovascular disease, and when sufficient observation has shown that a spontaneous return to normal will not occur. In certain carefully selected cases whose chief complaint is intractable palpitation even after adequate digitalis has been administered, quinidine treatment may be warranted. We are inclined to believe that quinidine is occasionally indicated in certain otherwise hopeless cases where all other means of therapy have failed to produce a response. Such situations are well illustrated by the extremely gratifying results obtained in the following two cases.

Van Nuys [30] reported a case of fibrillation in a male, 64 years of age, who had dyspnea, edema, cough and precordial pain despite large doses of digitalis. The heart was moderately enlarged and there was objective decompensation with an apex rate of 160 to 190. The patient became progressively worse despite ordinary therapy and as a last resort he was hospitalized and quinidine was given. After 4.4 gm. of the drug the heart rhythm became regular, but remained so only on a daily dose of 1.6 gm. During the period of experimentation he steadily improved despite frequent returns of arrhythmia; thus it is possible that the mere hospital routine played a part in his improvement. However, the quinidine dosage was gradually reduced and finally discontinued. He continued with a normal rhythm and was able to lead a quiet life feeling as well as he did before the onset of symptoms one year previously.

We had a similar case in our series. The patient was a 64 year old physician with hypertension and chronic myocarditis who had been a known fibrillator for five years. For one and one-half years before admission he had been having frequent attacks of angina pectoris and occasional nocturnal dyspnea. On admission he was cyanotic and orthopneic. The heart was enlarged and there were signs of marked congestive failure including edema, an enlarged liver and pulmonary congestion. He was irrational and breathing was of the Cheyne-Stokes type. Digitalis was given until toxic symptoms intervened when it was discontinued and quinidine therapy instituted. Although there was slight betterment of his condition before quinidine was given, a regular rhythm, following 2.5 gm. of the drug, produced almost miraculous response. Following his dismissal from the hospital, the patient again took up the practice of medicine and when last seen two and one-half years later was in good health with a regular heart rhythm and still conducting his medical practice.

Summary

An analysis was made of 49 cases of auricular fibrillation treated with quinidine sulphate. From observations made on these cases and from a review of the literature, the following conclusions can be drawn:

1. The question of reversion to a normal rhythm is not the only criterion necessary to judge the success of the treatment.

2. Sex is of no importance in this problem and age enters into consideration only in so far as older patients are somewhat more apt to have mural thrombi.

3. From an etiological point of view, rheumatic valvular disease is most resistant, non-valvular fibrillation responds more readily and in cases of hyperthyroidism without cardiovascular disease treated postoperatively, reversion to normal rhythm is practically invariable.

4. Duration of fibrillation influences to some extent the likelihood of reversion. Those cases in which there is a short history of fibrillation revert

more readily. A longer duration of fibrillation is more frequently attended with the presence of auricular thrombi and the danger of peripheral emboli.

5. The clinical condition of the patient proved to be no guide in avoiding disastrous results.

6. It is doubtful whether most cases are in better health with a regular rhythm than with auricular fibrillation when the ventricular rate can be kept slow.

7. An analysis of 62 autopsied cases of mitral stenosis has been made and statistical evidence is presented to prove that auricular thrombi are more frequent in fibrillating than in non-fibrillating hearts. It has been shown that the presence of fibrillation and increasing years are both separate factors favoring auricular mural thrombosis.

8. There seems to be no method of predicting the dire accidents that attend quinidine therapy such as sudden death and emboli for they occurred in patients who had been regarded as most favorable for quinidine treatment.

9. The four indications for the use of quinidine sulphate in chronic auricular fibrillation seem to be: (*a*) the presence of fibrillation in an otherwise normal heart, (*b*) its persistence after operation for hyperthyroidism, (*c*) when the irregularity is the cause of intractable palpitation and (*d*) in certain hopeless cases where other forms of treatment have failed.

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TRICHINOSIS

A REPORT OF EIGHT CASES WITH SKIN AND PRECIPITIN TESTS*

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Prior to 1928, a diagnosis of trichinosis was usually made by microscopic examination of tissue removed from a patient whose symptoms and blood picture had suggested that possibility. The utility of the skin and precipitin tests developed by Bachman in that year has been remarked by several later observers, and this report adds further confirmatory evidence regarding the accuracy and sensitivity of these tests.

The disease occurs more commonly than is generally known. The United States Public Health Service for the year 1932 reported 263 cases from 15 states. For the first nine months of 1933, 13 states reported 208 cases of trichinosis. From 1921 to 1928 the annual deaths from trichinosis in the registration area averaged 14 per annum. New York and California report more cases than any other states.

The New York State Department of Health in November 1933 reported in upstate New York 39 cases for the year 1930, 57 cases for 1931, and 21 cases for 1932. In the first 10 months of 1933, 74 cases were reported. This is three times the number of cases of the preceding year. In my own county (Suffolk, New York) no cases were reported in the last four years.

In regard to the general incidence of trichinosis, reported and unreported, it may be noted that Williams in 1901 reported an incidence of 5.34 per cent of trichinosis in 505 autopsies. In 1931, Queen, in 344 routine autopsies in Rochester, New York, found 17.5 per cent positive by a digestion method of examination of the diaphragm muscle. More extensive use of the Bachman tests will undoubtedly reveal many cases of this disease which would otherwise have remained undiagnosed.

The cause is the *Trichinella spiralis*. The mode of infection is through the ingestion of raw or insufficiently cooked pork. The carriers are the hog and the rat, and infection in mankind is accidental and does not result in further infestation. The trichinella is liberated when the trichinous wall is digested in the stomach and the fertilized female liberates the embryo into the lymph spaces of the mucosa of the intestines. From thence they go to the blood and are distributed to the muscles. The worm has been found in the spinal fluid, blood, stool and muscle.

There are three stages. The first or infestive stage is immediately followed by vomiting, diarrhea or constipation, and abdominal pains with hyperpyrexia. There are also muscle pains and prostration. The second

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stage is due to the invasion of the blood stream and is characterized by edema of the face and eyelids, less elevation of temperature, swelling of muscles, bronchitis and prostration. This period lasts about three weeks. The third stage is the stage of encystment, which occurs within the fifth and sixth weeks and is characterized by weakness and edema of the face and extremities. The temperature is usually normal.

The disease has been mistaken for typhoid fever, chronic rheumatism, sinusitis, grippe, acute nephritis and other diseases. The characteristic laboratory finding that usually calls attention to the diagnosis is eosinophilia, sometimes as high as 60 per cent or more. In the early stages with extreme hyperpyrexia there may be leukocytosis without eosinophilia. The treatment is symptomatic, and although many drugs are recommended, it is generally believed that none is specific. Salzer has reported curative action with convalescent serum, but this has been contradicted.

Case Reports *

Of the eight cases here reported five occurred in one group. These five patients were employed in one institution, and ate their meals together. Of the other three cases, two were in the same family (mother and son). The third, as far as is known, was not connected with other cases.

First Group

As noted above, these five patients ate their meals together. Apparently the food ingested was thoroughly prepared, the pork being fried or broiled; and when at times sausages were eaten these were well baked. Moreover, three other girls partook of the same food at all times, only one of whom developed symptoms. This institution catered to about 50 guests, none of whom became ill. A possible explanation for this may be that the guests ate after the employees, and in this way the pork and sausages they consumed had been given additional baking or frying.

Case I

J. W., female, white, aged 25; occupation, cook. This patient came into my office on September 24, 1933, complaining of swelling of the eyelids and of a burning sensation in both eyeballs. The lids were so edematous that it was painful to open and close the eyes, and the eyelids were so tight that the upper eyelid could not be everted. Her temperature was normal and she had no other symptoms. Three days later she had a temperature of 101° F., and complained of marked weakness, pain in the neck muscles and general bodily aches and pains. She continued to complain of swelling of the eyelids. A blood count on October 2 showed: W.B.C. 7,600, P.M.N.'s 49 per cent, P.M.E.'s 25 per cent, and lymphocytes 26 per cent. The stools were negative for parasites. Another differential count on October 3 showed the following: P.M.N.'s 64 per cent, P.M.E.'s 18 per cent, and lymphocytes 18 per cent.

* In the preparation of the following cases, I wish to thank Dr. A. Angrist and Dr. W. H. Ross for their kind assistance. I also wish to thank Mr. R. Smith of the Southside Hospital Laboratory, and the New York State Laboratory for their assistance.

She was ordered to bed and her temperature varied from 100° to 101° F. Gradually the fever subsided so that she was able to go to work after 11 days. Even while working she still complained of swelling of the ankles, weakness of the thighs and legs, and swelling of the eyelids for another two weeks until she fully recovered.

Case II

M. B., female, white, aged 25; occupation, maid. The onset of her illness was on September 24, when she complained of swelling of the eyelids, weakness, and fever (of 101° F.). She was sent home and did not ask for medical care until September 27 when she came into my office, complaining of swelling of the eyelids, upper part of the face and lips. She had no fever at that time, and complained of a sore throat. She said that she felt as though she had a cold. Physical examination was essentially negative. A differential count showed the following: P.M.N.'s 31 per cent, P.M.E.'s 48.3 per cent, and lymphocytes 19.7 per cent, large mononuclears 0.7 per cent.

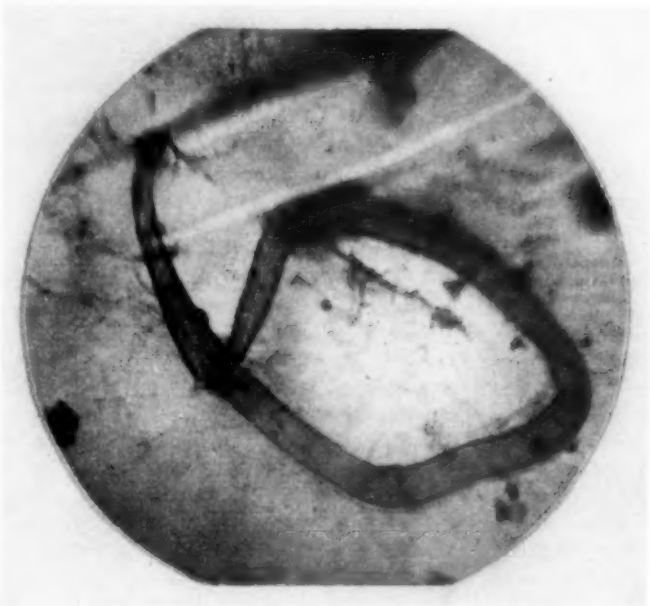

Fig. 1. Patient M. B. *Trichinella spiralis* in hemolyzed blood. High power.

A microscopic examination of blood hemolyzed in 3 per cent acetic acid, revealed *Trichinella spiralis*. (Figure 1.) She continued to have a low grade fever from 100° to 101.5° F. daily, complaining of weakness, pains in the muscles of the calves of the legs, and swelling of the ankles, until October 16 when she returned to work. Since then her course has been uneventful.

Case III

G. S., female, white, aged 21; occupation, waitress. This girl was sent home from work on September 27 because of swelling of the face and eyelids. She had a fever of 101° F. I saw her two days later, and she presented the same picture. She also complained of weakness, backache, and that the muscles of her jaw were painful.

She felt as though she had a toothache. She had vomited twice, but had had no diarrhea. There was pain on flexion of the head backward or forward, and intense headache aggravated by any movement. There was a positive Babinski sign on the right side and both knee jerks were elicited with difficulty. A blood examination on October 1 showed: R.B.C. 4,800,00,, Hgb. 90 per cent, W.B.C. 9,000, P.M.N.'s 44 per cent, P.M.E.'s 37 per cent, and lymphocytes 19 per cent.

She continued to have a low grade fever, and on October 4 small nodules appeared on the extensor surfaces of both forearms just above the wrists; they were about the size of a 10 cent piece and were surrounded by an inflammatory areola. These nodules (one on each forearm) disappeared in 24 hours. On October 7 she became very ill, her temperature reached 104° F., and she complained of severe pains and aches all over her body. She had a harsh cough and both lungs revealed bronchitis with coarse râles throughout. A blood count on that day showed: W.B.C. 21,000, PM.N.'s 56 per cent, P.M.E.'s 13.3 per cent, and lymphocytes 30.7 per cent.

Examination of stool on October 9 was negative for parasites and stool cultures were negative for typhoid. She continued to have a high fever for several days. The swelling of the eyelids and face gradually disappeared, and the bronchitis improved. The temperature became normal and on October 16 she returned to work. She felt weak for the following month, complaining of muscle aches and pains and swelling of the ankles until she gradually recovered.

Case IV

H. L., female, white, aged 23; occupation, second cook. On September 29 she became ill, complaining of swelling of the eyelids and face, and aches and pains all over her body. She felt very weak, had an intense headache and experienced difficulty in moving her jaw. She had vomited twice but had no diarrhea and no abdominal pain. Her temperature was 101° F. On October 3 a differential count revealed: P.M.N.'s 59 per cent, P.M.E.'s 29 per cent, and lymphocytes 12 per cent. Another blood count on October 6 revealed: P.M.N.'s 50.5 per cent, P.M.E.'s 27 per cent, lymphocytes 20.5 per cent, and large mononuclears 2 per cent. A specimen of blood was tested for agglutination with *B. abortus* and was negative. A Widal showed a doubtful reaction which was probably due to the patient having had typhoid vaccine previously. Her temperature was about 101° F. On October 9 when she returned to work she had improved a great deal; her temperature was normal but she still had a fine tremor of the hands and a slight urticarial eruption on the arms.

After she returned to work she still had several episodes of illness. On October 14 she vomited twice and felt very weak. When seen on October 22 she complained of pains in the calves of the legs, tremor, and nightmares.

She had lost 10 pounds. On October 28 she still complained of swelling of the ankles and calves. She had morning headaches and her eyes appeared bloodshot. She continued working, however, and made a steady improvement.

Case V

G. H., female, white, aged 24; occupation, chambermaid. On October 1 the patient complained of slight swelling of the eyelids, weakness and muscle pains. She had an intense headache and pain on flexing or extending the head. Her temperature was normal. The following day her entire face became swollen, especially the upper lip, so that her appearance was quite alarming. She developed an urticaria of the entire body which became more prominent or faded, advanced or receded from day to day, lasting for several days. This patient had been seen about a month previously when she had had a slight urticaria and had been cautioned against eating meats. In spite of this she had taken a small amount of pork occasionally. On October 3 a

blood count showed: P.M.N.'s 66 per cent, P.M.E.'s 19 per cent, and lymphocytes 15 per cent. Another blood count on October 6 revealed: P.M.N.'s 52.5 per cent, P.M.E.'s 14.5 per cent, lymphocytes 30.5 per cent, and large mononuclears 2.5 per cent. No agglutination was obtained with *B. abortus* and the Widal reaction was doubtful. (This patient had also had typhoid vaccine previously.) She continued to complain of muscle pains and weakness and ran a low grade fever, 100° to 101° F., until October 16 when she felt well enough to return to work. I saw her a week later on October 22, and she still complained of pains and weakness in the knees and dizziness when lying down. Her temperature was normal. On October 28 she still had slight weakness, her arms ached occasionally, but she felt much better. Thereafter she continued to improve and made a gradual recovery.

Second Group

Case I

P. K., male, white, school boy, aged 16 years. This patient was first seen on October 10, 1933. He complained of pain on moving his neck forward or backward, and his eyelids were swollen. He looked extremely toxic and had a temperature of 104° F. Physical examination revealed coarse bronchial râles anteriorly. He had a suggestion of a positive Kernig sign of both lower extremities. His symptoms suggested some meningeal or encephalitic lesion, but on account of the swelling of the eyes and the history of coincidental sickness of the mother who also had swelling of the eyelids, a blood count was taken which showed a marked eosinophilia of 25 per cent. The boy felt much better the following day. His temperature was only 101° F., and although he still had swelling of the eyelids and pains in the calves of the legs, the other signs were gone. He continued to improve and on October 17 his temperature was normal. He still felt extremely weak, however, and had generalized muscle and joint pains, especially in the muscles of the calves of his legs. On October 23 while attending school he noted that both his hands were swollen, and large nodules appeared above the wrist on the dorsum of each forearm. A blood count on that day showed: P.M.N.'s 37.7 per cent, P.M.E.'s 46.7 per cent, P.M.B. 0.3 per cent, lymphocytes 14.3 per cent, and large mononuclears 1 per cent.

The swellings of the hands and wrists disappeared within 24 hours, and the patient recovered without further complications. A biopsy from the calf muscle was negative for *Trichinella spiralis*.

The family denied eating pork, but gave a history of having eaten sausages the week prior to the onset of the illness. These sausages were bought from a chain butcher shop, and were apparently fairly well cooked.

Case II

M. K., female, white, housewife, aged 60, mother of P. K., the foregoing case. This patient became ill about October 6. She had severe diarrhea and swelling of the eyes for three or four days. She had pains in all her muscles, especially in the calves of the legs, and her ankles were swollen. On examination on October 10 she had a fever of 101° F. She had paid no attention to her symptoms and thought that she had "grippe." The presence of eosinophilia in her son's blood caused a blood count to be taken, and her blood also showed 25 per cent of eosinophiles. This patient was not as sick as her son and made a quicker recovery, the entire illness lasting only about one week. An interesting point was that the father who takes a glass of liquor with his meals and who also ate the sausages, had no symptoms.

Third Group

Case I

F. M., male, white, aged 32, married; occupation, iceman. This patient dates his illness to October 16 on which day he ate some pork chops in a lunch wagon; he mentioned afterward that they were not well done. He has also been in the habit of eating uncooked pork salami. On October 17 he complained of headaches, swelling of the eyes and extreme weakness. He had severe pains in the muscles of the back. I first saw him on October 19, and his entire face looked swollen, especially the eyelids. He had difficulty in extending and flexing the head. He had a fever of 101° F. He also mentioned that he had taken several aspirin tablets for a very intense headache, without relief. A blood count on October 20 showed: P.M.N.'s 70 per cent, P.M.E.'s 10.5 per cent, lymphocytes 17.5 per cent, and large mononuclears 2 per cent. The patient continued to have a fever of about 101° F. for a week, while at the same time he developed attacks of extreme epigastric pains and tenderness, and was relieved only after catharsis and the use of sedatives. Another blood count on October 28, when the patient's temperature was normal, showed: P.M.N.'s 47.5 per cent, P.M.E.'s 21.5 per cent, lymphocytes 29 per cent, and large mononuclears 2 per cent.

The patient continued to complain of extreme weakness and muscle pain for another two weeks, and then gradually made a recovery.

Skin Tests

On November 11 a series of skin and precipitin tests was done on these cases. The antigen (Bachman's) was obtained through the courtesy of Dr. Benjamin Schwartz of the U. S. Department of Agriculture.

In the markedly positive cases a wheal presented itself at the site of intracutaneous injection within 10 to 15 minutes. This was raised, about three-eighths to one-half inch in diameter, and showed the presence of pseudopods. There was surrounding inflammation about this raised area which was red and angry looking. This reaction persisted sometimes for 24 hours. Coca's solution (sodium chloride 0.7 per cent, sodium bicarbonate 0.05 per cent, phenol 0.4 per cent) was used as a control. Bachman's antigen in Coca's solution was used in dilutions of 1–100, 1–1000 and 1–10,000. (Figure 2.)

It may be noted from the foregoing results that skin tests were markedly positive in the first seven cases listed, and definitely positive in the eighth case. In regard to the control tests done on non-trichinous cases negative results were obtained in all cases except one (R. K.) which gave positive reactions in all dilutions and also was markedly positive to Coca's solution. This patient was possibly phenol sensitive. It is to be noted also that two patients who had markedly positive Wassermann tests did not react to the Bachman antigen.

Precipitin Tests

Precipitin tests were also done according to the method of Dr. George W. Bachman, using his antigen in Coca's solution and floating it in various dilutions above the serum to be tested.

Right Left

FIG. 2. Right forearm showing positive reactions, reading from above downward in 1-100, 1–1000, and 1–10,000 dilution of antigen. Left-arm: Coca's solution; no reaction. Test done on patient P. K. (Photo from painting in watercolor.)

RESULTS OF SKIN TESTS ON PATIENTS

Patient	Diagnosis	Estimated Day of Illness	1–100	1–1000	1–10,000	Coca's Solution
J. W.	trich.	47	++++	++++	++++	–
M. B.	trich.	47	++++	++++	++++	–
G. S.	trich.	44	++++	++++	++++	–
H. L.	trich.	44	++++	++++	++++	–
G. H.	trich.	42	++++	++++	++++	–
P. K.	trich.	32	++++	++++	++++	–
M. K.	trich.	32	++++	++++	++++	–
F. M.	trich.	27	++	++	++	–
Control Tests on Non-Trichinous Cases						
C. K.	diabetes		–	–	–	–
J. S.	cardiac		–	–	–	–
M. K. K.	cardiac		–	–	–	–
L. J.	lues		–	–	–	–
R. K.	chr. mastoid		++++	++++	++++	++++
F. deO.	lues		–	–	–	–

It is evident from these tabulated results that the precipitin test in trichinous patients does not yield as definitely positive results as does the skin test.

As stated above, the use of these tests began in 1928, when George W.

RESULTS OF PRECIPITIN TESTS ON PATIENTS

Pt.	Diag.	Day	1–100	1–500	1–1000	1–2000	1–5000	1–10,000	Coca's Solution
J. W.	trich.	47	not done						
M. B.	trich.	47	+	+	−	−			−
G. S.	trich.	44		±	−	−			−
H. L.	trich.	44	−	−	−	−			−
G. H.	trich.	42	+	+	−	−			−
P. K.	trich.	32		+		−	−	−	−
M. K.	trich.	32	+	−	−	−			−
F. M.	trich.	27	−	−	−	−			−
Control Tests on Non-Trichinous Cases									
J. S.	cardiac		−	−	−	−			−
M. K. K.	cardiac		−	−	−	−			−
L. G.	urticaria		−	−	−	−			−
R. K.	chr. mastoids		−	−	−	−			−
F. deO.	lues		−	−	−	−			−

Bachman was able to produce a satisfactory antigen of the *Trichinella spiralis* for precipitin tests, and showed the appearance of precipitins after the thirtieth day in experimental infection with rabbits. He also demonstrated precipitins in the serum of man infected with *Trichinella spiralis.*

Again in 1928 he showed the presence of a local skin reaction specific in character following the intracutaneous injection of *Trichinella spiralis* protein. These skin reactions appeared as early as the second day after feeding trichinous meat experimentally to rabbits. Again in 1928 he confirmed the previous work in regard to skin tests using 1–100 dilutions and showed the presence of precipitins experimentally 20 to 30 days after infection. He therefore advised the use of skin tests rather than precipitin tests, as the skin test was easier to do and appeared much earlier. In 1928 Bachman simplified his precipitin test using Coca's solution with his antigen instead of a neutralized antigen of definite H ± ion concentration. He also regarded the antigen in Coca's solution as more potent, precipitins being detected some five to 20 days after infection. In a study of complement fixation in experimental trichinosis Bachman and Menendez demonstrated the presence of antibody formation in rabbits 25 days after infection.

In 1929 Stoll reported the application of the precipitin test in three cases of human trichinosis. Bachman obtained positive reactions in all three cases in high dilutions.

Hunter in 1931 demonstrated precipitins in three cases of human trichinosis with indefinite or negative results in three other suspected cases. Swineford and Waddell used skin tests in five cases of trichiniasis and obtained positive reactions.

Augustine and Theiler in 1932 found the precipitin test to be reliable in detecting trichinosis in swine and to be highly specific. They also found that although trichinosis in man was invariably detected by the precipitin

test, the diagnostic value of the test was diminished by the fact that it was also positive with individuals who had recently taken quinine. They regarded the intradermal test as specific for trichinosis in man and swine in high dilutions up to 1–10,000 and higher. They also found precipitin and intradermal tests more accurate than muscle examination in the swine.

In 1933 McCoy, Miller and Friedlander tested a series of 88 persons who were said to have had trichinosis with skin tests. They obtained immediate positive reactions in 92 per cent of cases within two to six weeks after infection. From that time on, the greater the period that elapsed between infection and skin test, the less the number of positives. In persons ill three and one-half to seven and one-half years prior to the tests, only 62 per cent were positive. They also did control tests on 104 persons and showed an incidence of only 4 to 6.5 per cent positive. They also showed that persons infected with *Trichuris trichiura* gave 18 per cent of positives in 1–10,000 dilutions and 62 per cent positives in 1–500 dilutions. They regarded the latter reactions as a group reaction of a related parasite.

Discussion

In a review of 137 cases reported in the literature since 1928, in which the reference is made to the source of infestation, I find that in only 22 cases was the cause given as uncooked pork. Of these 22 cases 13 ate pork bologna or smoked ham and only 9 ate raw pork or raw sausage. So that while no brief is held for raw pork, it must be stated that most of the cases of trichinosis that did occur were due to improperly cooked pork.

In view of the fact that no specific therapeutic agent has as yet been found, in spite of repeated attempts at intravenous medication, the treatment must still be symptomatic. The encystment of the parasite by the connective tissue and calcium results in a regression of symptoms. Calcium could therefore be given after the first week or 10 days. Marked lowering of the blood pressure is a feature of severe trichinosis, and in such cases vasomotor stimulation is of course indicated.

McCoy in 1931 showed that rats developed immunity to *Trichinella spiralis* and that they were able to withstand more than twice the lethal dose of larvae. This immunity was a comparative rather than a total immunity. In 1932, in studying the length of adult life of *Trichinella spiralis* in rats, he showed that the dose of infection influenced the length of time the adult worms persisted in the intestine. There are, however, two factors to be considered. One is resistance to the exotoxin and the other is the resistance to the migration of the organism itself. While there is hope of producing a serum capable of an antibody response to the exotoxin, the migration of the larvae through the blood and tissues will probably have to be controlled by chemical agents.

Miller, McCoy and Bradford in 1932 questioned the therapeutic value of arsphenamine derivatives and antimony and potassium tartrate in the treatment of human trichinosis. They also tried out a host of other therapeutic agents with no beneficial result.

It has been found that trichuris, a related organism to trichinella which gives group reactions in concentrated dilutions to trichinosis antigen, is readily affected by oil of chenopodium in the intestinal tract. I have therefore used oil of chenopodium in the early stages after initial purging. I have also given calcium gluconate by mouth after the first week following the onset of symptoms, and adrenalin as indicated, especially where there is marked edema of the face and eyelids.

In the past, physicians have been perhaps hesitant in reporting possible cases of trichinosis, especially in the rural districts as they have had little access to pathological laboratories where muscle sections could be studied. At the same time others have hesitated due to the difficulty in obtaining permission for biopsy. With the use of the new intracutaneous test of Bachman many more cases will probably be reported, as the diagnosis may be made much more accurately.

The intracutaneous test is easier of application and more definite in its results. It is also obtained earlier. However, it has the one drawback that repeated tests sensitize the individual to the antigen so that subsequent tests become positive even in normal persons. If a negative skin test is obtained a subsequent positive one would be doubtful. The main recourse would then lie in the precipitin test and the further refinement in the ease of application of this test is to be looked forward to.

In any discussion of this disease, its prevention must be considered. The best prophylaxis is the thorough cooking of pork. There is no inspection by the Department of Agriculture, with a view of detecting the trichinae. It has been found that in Germany of 6329 cases of trichinosis with 318 deaths, 2042 cases and 112 deaths were from meat that had been examined and released for trade as free of trichinae. The inspection must be microscopic, and cases are frequently missed in spite of elaborate systems of inspection. (Tice.)

Pork products usually eaten without cooking are processed under the following regulations when they originate in establishments under federal supervision. They are so cooked that all parts of the products attain a temperature of not less than 137° F. (59° C.) or refrigerated for a period of not less than 20 days at a temperature of not higher than 5° F. (minus 15° C.) or prepared with special curing methods of known effectiveness in killing trichinae. Augustine in 1933 has demonstrated that raw pork in commercial communities may be rendered safe as far as trichiniasis is concerned by either rapidly lowering its temperature to minus 35° C. or by rapidly lowering its temperature to minus 18° C. and maintaining that point for at least 24 hours. As to the possibility of using the intracutaneous test for trichinosis on hogs, in spite of its efficiency it is doubtful whether this method of prophylaxis will prove practical.

Conclusions

1. Eight cases of trichinosis are reported with recovery.
2. In all cases infestation occurred from cooked pork or sausage.

3. Edema of the eyelids, intense headache and pain on flexing or extending the neck were outstanding features of all cases.

4. Skin tests were positive in all cases in 1–100, 1–1000, and 1–10,000 dilutions. Precipitin tests were also done with less positive results.

5. Mild trichinosis may be very easily overlooked or mistaken for grippe or other infectious diseases.

6. Trichinosis may be found in scattered cases as well as in large groups.

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PAROXYSMAL AURICULAR FLUTTER WITH 1:1 AURICULO-VENTRICULAR RATIO*

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Introduction

Auricular flutter with a ventricular rate of 70 to 160 a minute is a common condition and is met with, according to McMillan and Bellet,[1] once in every 80 cases of heart disease or of suspected heart disease; but auricular flutter with ventricular rates above 200 are quite rare. The rate of auricular contractions in flutter ranges from 220 to 400[2] or over, in untreated cases, while the ventricular response is usually slower. The auriculo-ventricular ratio is 2:1, 3:1, or 4:1; rarely it may be 6:1 or 8:1 as in cases of complete block.[3] At times the ventricular response is irregular. Very rarely, the refractory period of the A–V node suddenly decreases and the junctional tissue becomes extremely sensitive to the auricular stimuli, transmitting all of them to the ventricle. In such instances an extremely rapid heart rate follows.

Such changes in the refractory state of the A–V node and in the irritability of the junctional tissue take place in auricular paroxysmal tachycardia, where ventricular rates as high as 250 have been reported.[4] Rarely such phenomena occur in auricular fibrillation, although here not all the auricular stimuli are transmitted by the junctional tissue. Nevertheless ventricular rates of 220 have been reported.[4] A similar condition with rapid transmissions of impulses by conducting tissue, though perhaps in the opposite direction, occurs in paroxysmal ventricular tachycardia where rates of 200 to 300 have been recorded.[5–8] The best example of this mechanism is observed in auricular flutter with an established 2:1 auriculo-ventricular ratio, where suddenly the refractory period of the A–V node becomes shorter than the auricular cycle. A sudden doubling of the ventricular rate follows and a 1:1 rhythm, or a 1:1 auriculo-ventricular ratio, is established. In some cases, however, the auricular flutter and the 1:1 ventricular response begin simultaneously in a paroxysmal attack.

Theoretically, heart rates between 200 and 400 may be expected when the ventricle takes up the rate of the fluttering auricle. It seems, however, that the junctional tissue cannot transmit stimuli faster than about 300 per minute, for these are the highest rates recorded in the human heart.[8, 9] According to Lewis,[10] this is not only because the junctional tissue is unable to transmit impulses at such a fast rate but also because stimuli coming so fast are poorly conducted. Thus in auricular rates above 300 to 350 a 2:1 block is established. When the auricular rate drops below 300, conduction

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improves, and if the junctional tissue is sensitive enough to transmit all stimuli, the ventricular rate is the same as the auricular rate and a 1:1 rhythm ensues.

The usual heart rates in auricular flutter with 1:1 ventricular response are 220 to 300. Blackford and Willius [9] reported a rate of 320 in one case, but this was estimated by counting through a stethoscope; the electrocardiographic rate of the same patient was 300 or slightly over. Such rapid rates last from several minutes to several hours, and very rarely for several days. Alarming symptoms are usually ushered in, such as palpitation, precordial pain, pulmonary edema, and syncope. In rare instances, death may ensue, as in the case reported by Bourne,[11] where a rate of 260 lasting seven days in a woman of 28, ended fatally from coronary occlusion by an embolus from an antemortem clot in the left auricle.

A similar case is here reported, though in this instance the patient recovered from the attack.

Case Report

An American seaman, a radio officer, age 48 years, was admitted to the U. S. Marine Hospital, Ellis Island, April 20, 1933. His chief complaint was shortness of breath and palpitation. The family history was unimportant. Habits were moderate. There was no history of childhood diseases; no rheumatic fever or chorea. The patient denied luetic infection.

For the past 10 to 15 years he had been having periodic attacks of palpitation, and for the last four years he had noticed that he had shortness of breath on exertion and that the attacks of palpitation were becoming longer, lasting about a half hour and recurring more frequently. However, he was never much handicapped by these symptoms. Three weeks before admission to the hospital, after returning to his ship from a mountain climbing trip, while the ship was in port, he was seized with severe palpitation followed by shortness of breath and a constriction of his chest, the like of which he had never experienced before. He was in great distress but had no characteristic precordial pain. By the time the ship surgeon was able to see him he had improved somewhat but began to bring up frothy, pink sputum. He was given injections and was ordered to stay in bed. Shortness of breath continued and a week later, while in bed, he developed another attack of palpitation associated with cough, and pink frothy sputum. This attack was not as severe as the preceding one. Improvement followed and the patient came to the hospital two weeks later, that is, three weeks after the first attack.

On admission he brought a note from the ship surgeon stating that the patient had had two attacks of pulmonary edema and that during these attacks the pulse was 120 to 130. He had responded well to hypodermic medication of morphine and atropine, and intravenous digitalis. The pulse had dropped below 90 each time following the medication. In the period of 10 days he had been given digitalis equal to three-fourths of the estimated dose required for digitalization; and as the patient improved, the drug had been discontinued.

On examination in the hospital the patient appeared well developed and well nourished and did not look ill, except for moderate dyspnea. The general examination was negative except for poor condition of the teeth and for a small inguinal hernia. The heart was slightly enlarged to the left, the sounds were distinct, there was no gallop rhythm and there were no murmurs. The rate was 76 and the rhythm was regular. The lungs were clear, the liver was not enlarged and there was no edema of the ankles. There was no evidence of peripheral arteriosclerosis. The blood pres-

sure was 144 systolic and 90 diastolic, and the temperature 37° C. The urine showed a faint trace of albumin and rarely a hyaline cast. Hemoglobin was 80 per cent, red cells were 4,400,000 and white cells 8,000 per cu. mm. The differential count was normal. The blood Wassermann was negative. Roentgen-ray film and fluoroscopic examination of the heart showed it to be moderately enlarged to the right as well as to the left. The retrocardiac space was normal. The electrocardiogram showed left axis deviation, slight elevation with modified cove planing of the (S–T) segment in Lead I, faint elevation of $(S–T)_2$ and $(S–T)_3$, and P_3 was diphasic. The chest lead (the right electrode posteriorly and the left electrode anteriorly) showed distinct elevation of the (S–T) segment. The rate was 84. (See figure 1.)

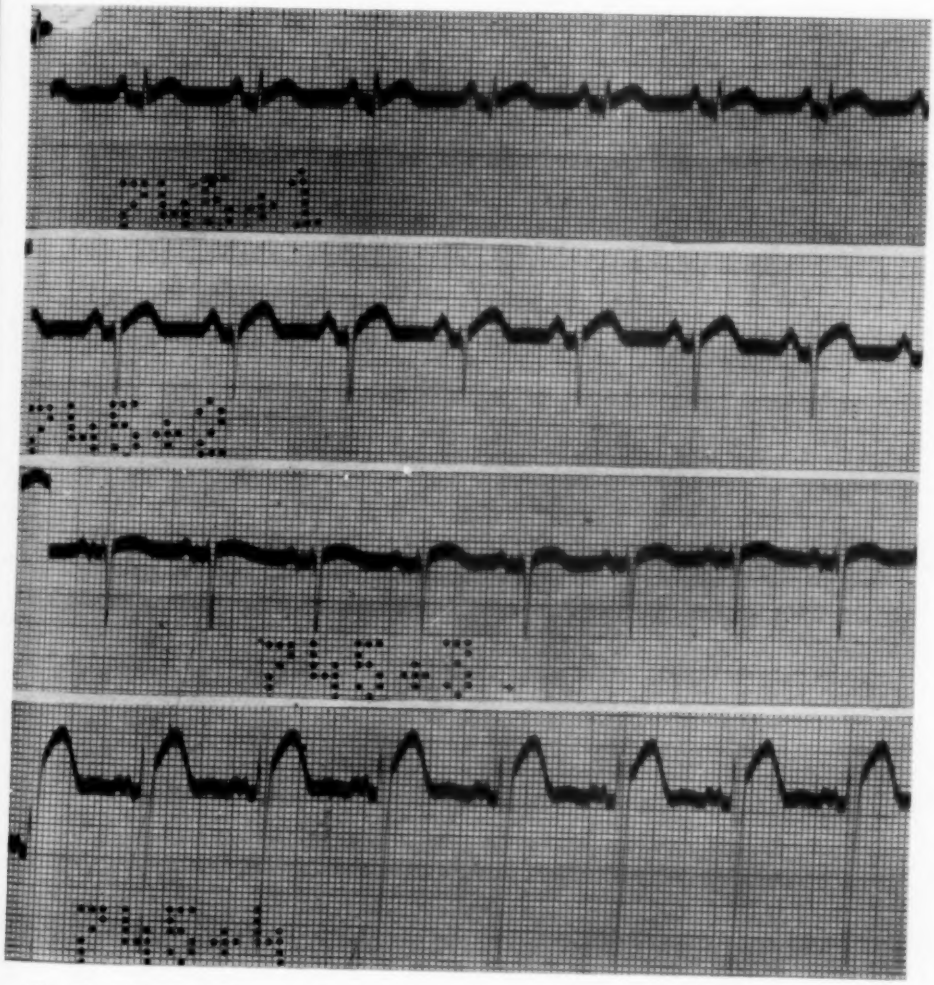

FIG. 1. Electrocardiogram taken on the day of admission showed elevation with modified cove planing of the $(S–T)_1$ segment, faint elevation of $(S–T)_2$ and $(S–T)_3$ and P_3 was diphasic. There was left axis deviation. The chest lead taken with the right electrode posteriorly and the left electrode anteriorly showed distinct elevation of the (S–T) segment. The rate was 84.

The admission diagnosis was: Paroxysmal tachycardia with pulmonary edema and recent myocardial damage due to coronary occlusion. The patient was put on

mild sedatives and allowed to be semi-ambulatory. Two weeks after admission he stated that his palpitation began to reappear, usually at night, lasting 15 to 30 minutes. On two occasions he had pain in the region of his heart. His pulse rate during the palpitation was recorded by the night nurse as 120. Electrocardiographic tracings showed no change except slight flattening of T_3 and pointing of T_1 and T_2. He was given digitalis by mouth with the hope of reducing the frequency of his palpitation. He received 35 grains in 17 days. During this time he was doing very well, had no precordial pain or palpitation. The heart findings were about the same as on admission, except that at times a systolic murmur was heard at the base. Electrocardiogram showed no digitalis effect. On June 5, in the afternoon, he suddenly developed severe palpitation associated with pallor, cold perspiration, and moderate dyspnea. The heart rate was very rapid and could not be correctly estimated. It was approximately 250 a minute and regular. Vagal pressure as well as pressure on the eyeballs at this time had no effect. He was given a hypodermic injection of morphine, an ice bag to his precordium, and was put to bed. (See figure 2.)

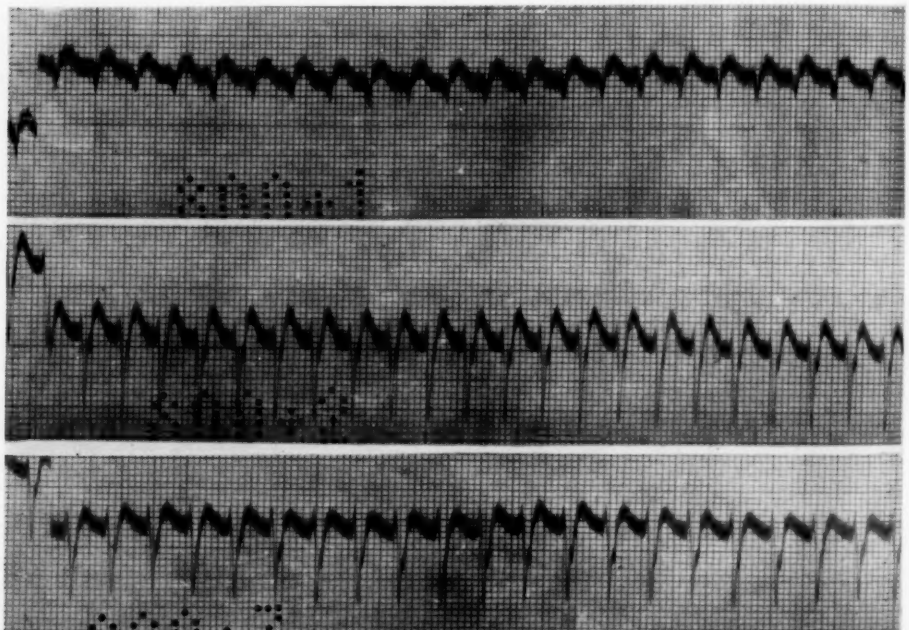

FIG. 2. Electrocardiogram taken about a half hour after onset of tachycardia showed a rate of 240 with a regular rhythm. The appearance of the complexes suggested auricular flutter with a 1 : 1 auriculo-ventricular ratio.

Electrocardiographic tracings taken during this paroxysm of rapid heart action showed a rate of 240 with a regular rhythm. The appearance of the complexes suggested auricular flutter with a 1 : 1 auriculo-ventricular ratio. This rate continued for about two hours, after which it was recorded by the nurse as 120. Unfortunately an electrocardiogram was not taken during this halved rate. A tracing on the following morning showed a rate of 76, with complexes essentially the same as had been recorded before the onset of his rapid rate. Physical examination of the heart revealed no change and the patient was free from symptoms. He remained in the hospital for another week without recurrent attacks of tachycardia, and left for home while he was still moderately dyspneic on exertion.

About eight months later the patient reported by mail that he had not been able to return to work. His attacks of palpitation and shortness of breath were likely to occur on the slightest exertion. He had many attacks of the "milder type" and "two of the extremely rapid heart fluttering type with pink sputum." On several occasions he was able "to ward off an attack of the extremely rapid type by bending forward when the heart seemed undecided whether to go back on its regular beating or to take up the very fast palpitating route."

Comment

Although no electrocardiographic tracing has been obtained of the patient prior to admission, it is reasonable to assume that the "mild attacks" of palpitation with rates of 120 to 130 (half that of the subsequent 1 : 1 rhythm) were attacks of paroxysmal auricular flutter with a 2 : 1 auriculo-ventricular ratio. Since it is sometimes difficult to differentiate electrocardiographically between paroxysmal tachycardia of very high rate and regular rhythm, and that of paroxysmal auricular flutter with a 1 : 1 ratio as in the case of Bunn,[8] the mild attacks of this patient with a rate exactly one-half of the one recorded during his hospital stay, help in a measure and lead to the diagnosis of previous paroxysms of auricular flutter. The electrocardiographic findings during the normal rate, the history of a sudden onset of severe shortness of breath with constriction of the chest, which occasioned admission to the hospital, and the subsequent dyspnea and disability strongly suggest a coronary occlusion and occurrence of pulmonary edema, during the paroxysm of tachycardia. As stated above, only one case was found in the literature where a coronary occlusion occurred during a prolonged attack of auricular flutter in a case of 1 : 1 rhythm. It is supposed that this case is of similar nature with probably a less extensive occlusion. This case also adds one more to the small group where a 1 : 1 rhythm developed not during established flutter of 2 : 1 block as is usual, but as a paroxysm of 1 : 1 in a heart with normal rate and rhythm subject to paroxysms of 2 : 1.

The literature records only 29 instances of auricular flutter with 1 : 1 ventricular response, testifying to the comparative rarity of this condition. Eighteen of these were gathered from the literature by Parkinson and Bedford [12] in 1927. Bedell [13] in 1933 carefully analyzed 21 recorded cases, and added three to the list.

The incidence of 1 : 1 rhythm in auricular flutter is given by Bedell as 4 per cent of all flutter cases, while McMillan and Bellet [1] met with only two instances among 80 cases of auricular flutter.

The condition is paroxysmal and develops usually in cases of established flutter of 2 : 1 auriculo-ventricular ratio.[1, 9, 12, 14-22 and others] Bedell seems to reject those cases where only paroxysms of 1 : 1 rhythm were recorded, without previous evidence of established flutter. Since auricular flutter is not considered as established unless it continues for more than two weeks,[1, 12] a paroxysm of 1 : 1 ratio may very well develop during such an interval. Such instances are seen in the cases of White and Stevens,[23] Allan,[24] Parkin-

son and Mathias,[25] Bourne,[11] and in the case included herewith. Moreover the paroxysm of 1 : 1 ventricular response may arise in cases of auricular flutter even with 4 : 1 block as was clearly shown by Winterberg.[15]

The age limits of the reported cases are between 19 and 52. There are five instances in children below the age of 6, Koplik,[26] Poynton and Wyllie,[27] Lewis,[28] and Sachs.[29] According to Wilson,[30] however, it is difficult to distinguish auricular flutter of 1 : 1 auriculo-ventricular ratio in children from paroxysmal tachycardia of auricular origin. He classes these conditions as tachysystole. Bedell [13] thinks that in older individuals the junctional tissue cannot transmit stimuli as rapidly as in younger and middle-aged people, hence the rarity of 1 : 1 rhythm in individuals above 50.

Out of 29 cases gathered from the literature, 15 had no evidence of heart lesions. In six instances the authors did not state whether or not there was evidence of heart disease. The remainder of the cases were associated with rheumatic heart disease, hypertension, arteriosclerosis, hyperthyroidism, cardiovascular lues, and congenital heart disease. It is significant that whereas in established flutter the heart is damaged in about 90 per cent of the cases, and only one out of 65 was free from serious cardiac damage in McMillan and Bellet's series,[1] in paroxysmal 1 : 1 rhythm 50 per cent or over are free from cardiac lesions.

The ventricular rates in the reported cases ranged between 222 and 300. The onset of the paroxysm usually follows exertion and rarely may follow quinidine medication, as mentioned by Bedell with reference to Parkinson and Bedford's cases.[12] The duration of the attack varies from minutes to hours, and the symptoms vary with the ventricular rate. They are usually severe and may cause syncope, pulmonary edema, myocardial failure, and coronary embolism. However, two patients of Parkinson and Bedford and one of Blackford and Willius,[9] with heart rates of 254, 275, and 320, respectively, were able to be up and about for several hours without apparent distress. The effect of vagal pressure varies; more frequently it is of no help.

There are four deaths on record among 29 cases, only one definitely attributable to the tachycardia—the case of Bourne with the coronary occlusion. Of the two deaths in the series of Blackford and Willius, one had no electrocardiographic evidence of 1 : 1 rhythm, and the diagnosis in the other case was equally uncertain. The heart rate in Bedell's case was not known before death. The prognosis is guarded because the paroxysms tend to recur in greater frequency.

Auricular flutter with 1 : 1 ventricular response must be differentiated from the paroxysmal tachycardias of auricular as well as of ventricular origin. In the tachycardias the A–V ratios are naturally always 1 : 1, although in rare instances, as stated by White,[2] a temporary auriculo-ventricular or intraventricular block may develop. However, their rates are usually below 200, and the complexes on the electrocardiogram are not entirely uniform and regular. Furthermore they are usually initiated by an

extrasystole. In flutter with 1 : 1 response, however, the established A–V ratio prior to the paroxysm usually is 2 : 1. The ventricular rate is usually above 200 and frequently above 250.

Summary

A case of paroxysmal auricular flutter with 1 : 1 auriculo-ventricular ratio is presented, where a coronary occlusion and pulmonary edema are believed to have occurred during a previous paroxysm. The literature is reviewed of all the presumably recorded cases and the incidence of the condition, and the associated heart rates, symptoms and cardiac lesions are discussed.

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DERMATOMYOSITIS *

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Dermatomyositis was described by Steiner [1] as "an acute, subacute or chronic disease of unknown origin, characterized by gradual onset with vague and indefinite prodromata followed by edema, dermatitis and multiple muscle inflammation." If this description be amended to read "multiple non-suppurative muscle inflammation," it becomes definitive. Although the disease was recorded independently by E. Wagner,[2] Unverricht [3] and Hepp [4] in 1887, Steiner was able to collect only 28 undoubted cases in 1905. Since then some 75 additional instances have been noted, practically all in the English, German and American literature. Excellent reviews are those of Rosenthal and Hoffman [5] and Wheeler and Harbin.[6] Since the disorder may be acute, subacute or chronic, there is much variation in the details of symptomatology and pathology. Exact diagnosis is made more difficult by the many points of similarity which exist between chronic dermatomyositis, generalized scleroderma, calcinosis and myositis fibrosa and by the fact that mixed cases have been observed.[7, 8] Langmead [9] has made an interesting comparative analysis of the four conditions, and advances the theory that they are different and possibly sequential manifestations of a single morbid process. Certainly all gradations seem to exist between chronic dermatomyositis and generalized scleroderma.

Etiology

The etiology is quite indefinite. There is neither race nor sex predilection, and children are affected less often than adults. The disease seems to occur more frequently during the winter. Many cases have followed some type of acute infection, particularly of the upper respiratory tract. Some have occurred after gastrointestinal disturbances probably of toxic origin, while others have developed after severe exposure to cold. Numerous instances have appeared *de novo* in previously healthy individuals. Unverricht [3] thought that it might be due to infection with Gregarines on account of the similarity of the histological picture in dermatomyositis to that in canine gregarinosis. Recently an analogous suggestion was made by Theobold Smith,[10] who noted the similarity of the pathological findings to those in sarcosporidiosis of swine. Staphylococci and streptococci occasionally have been isolated from the muscles and from heart's blood obtained at necropsy. It seems likely that the syndrome may result from various infections and intoxications. The only group of cases suggesting contagion

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which has been observed, was reported by Sick [11] as occurring among the nurses at the Tübingen Psychiatric Clinic. Later observers have questioned the diagnosis in this group.

Symptoms

The onset may be acute with malaise and fatigue followed by muscle pains, local swelling and rigidity and fever. More often there is a prodromal period of one to three weeks during which the complaints include fatigue, vague rheumatoid pains, insomnia, anorexia and sometimes gastrointestinal disturbances. Pain begins more often in the legs and is followed by weakness and swelling. In the early stages the consistence of the muscles may be soft and doughy; but with the progress of the disease induration becomes more marked until in cases of long standing the affected musculature is hard and lumpy, with contractures and great limitation of movement. Muscular involvement is usually bilaterally symmetrical but may be limited to a single limb. The legs and arms are most frequently attacked, the flexor muscles more than the extensors, although the buttocks, abdomen, neck and face are often implicated. Less frequently myositis extends to the diaphragm, intercostal muscles, pharynx, tongue and external muscles of the eyes. Only rarely is there evidence of myocarditis. The tendon jerks are diminished but a reaction of degeneration is found in only the most chronic cases.

Edema appears early, as a rule with the onset of fever. It is most marked over the face and the involved muscles, it is brawny, seldom pits on pressure, is often bilaterally symmetrical and may attain striking proportions. The hands and feet are said never to swell. During the first few days of illness the skin even where no edema is present may be smooth and glistening. The eruption is multiform and may be erythematous, scarlatiniform, erysipeloid or urticarial. Some cases show lesions resembling erythema multiforme and erythema nodosum. Desquamation and pigmentation may follow the rash. At times the buccal or pharyngeal mucosa may be involved with production of ulcerative stomatitis or angina.

In the more severe and chronic cases, edema and muscle swelling are persistent with great loss of strength and development of contractures. Paresthesias may be troublesome and hyperhidrosis of the affected skin is frequent. Fever of variable degree and duration is the rule though afebrile cases have been described. The temperature is said never to exceed 104° F. The spleen has been enlarged in many instances, and is always described as very soft. The blood shows little of diagnostic value. Marked leukocytosis is exceptional and there is no constant change in the differential formula, although Wermer [12] reported a case in which eosinophilia of 38 per cent was present and McGarrahan [13] saw a patient whose eosinophiles rose to 29 per cent. There are no constant urinary findings. The basal metabolic rate has shown no significant modification.

Pathology

Changes found in the skin and muscles vary with the duration and severity of the disease. Grossly the muscles are pale red to yellow and may show yellowish-grey or diffuse reddish streaks. They are often moist and friable although the consistence may vary from boggy to almost ligneous. In early cases the microscopic picture is that of a parenchymatous and interstitial myositis, the fibers separated by edema and showing all stages of degeneration from finely and coarsely granular to hyaline, waxy or fatty change. Fragmentation is found and is perhaps the first evidence of degeneration. It is characteristic that the process is most irregular. Normal fibers are found among diseased ones or small areas of degeneration occur in apparently normal muscle. There are conspicuous interstitial perivascular accumulations of polymorphonuclear and lymphocytic cells. The walls of the blood vessels may appear thickened with the absence of any demonstrable proliferation of the vascular coats. In advanced cases there is much increase in connective tissue, the perimysium and endomysium being equally involved. Evidences of muscle regeneration are present and occasional normal muscle fibers may be seen in the midst of areas of newly formed connective tissue. In other instances the arterioles show intimal proliferation and hyaline degeneration, sometimes with occlusion. In the skin there is irregularity in the thickness and in the architecture of the epidermis with distortion of the papillae, and occasional hyperkeratotic follicles. The dermis shows edema and perivascular infiltration with round cells. The panniculus may be atrophic with hyaline degeneration of the collagen and cellular infiltration of the fat lobules. Deposits of calcium have been noted in three instances.[7] There are no specific pathologic changes in the viscera.

Diagnosis

During the acute stage dermatomyositis may so simulate trichinosis that several of the early case reports used the title " Pseudotrichiniasis." Fever and constitutional reaction are more severe and prolonged in trichinosis, the edema is softer, and swelling of the face and eyelids is apt to be more striking. Involvement of the extraocular muscles and of the musculature of the jaws and pharynx is more common. Skin changes aside from edema are neither prominent nor progressive. Leukocytosis and eosinophilia are not commonly features of dermatomyositis. Absence of a history of gastrointestinal disorder, failure to find larvae of trichinella in the stools and finally histological examination of a bit of muscle are most important in differentiation.

Scleroderma must be excluded in the more chronic cases. The absence of myositis is perhaps the only adequate criterion as the tendency is to classify all instances of sclerodermatous change in the skin associated with muscle infiltration as dermatomyositis. At times differentiation may be impossible.

Syphilitic myositis and various types of suppurative myositis may present problems of differentiation as also may polyneuritis and trophic neuroses. In none of these is the triad of eruption, edema and myositis present.

Prognosis

Approximately 50 per cent of the reported cases have ended fatally, some in as short a time as three weeks, and others after months. Death has resulted from respiratory failure or, more properly, suffocation when there was extensive disease of the respiratory muscles. Bronchopneumonia is the usual cause of death, frequently an aspiration pneumonia secondary to myositis of the pharynx. Heart failure the result of myocarditis has apparently been fatal in a few instances. Prognosis therefore is grave in all cases with extensive involvement of the muscles of deglutition and respiration, but in others it may be considered good. The disease may run an acute course with recovery or may progress from one group of muscles to another producing invalidism for as long as two years. Complete recovery has occurred after extensive contractures have developed.

Treatment

All methods of therapy have been ineffectual in the great majority of instances. Salicylates, quinine, calcium chloride and arsphenamine have been credited with isolated cures.

Case Report

H. B. (Unit No. 272), a white boy 14 years old, was admitted to the University Hospital December 16, 1932 complaining of generalized swelling and of soreness of the neck, jaw muscles, abdomen and back.

The family history was irrelevant; no other members of the family were ill. The past medical history included measles and chicken pox during infancy and frequent upper respiratory infections. Six days prior to admission there had been a superficial scalp wound which caused moderate hemorrhage but no particular discomfort.

The present illness began five days previously with coryza, occipital headache and general aching which persisted until the day before admission when there were chilly sensations, fever, and swelling of the face and legs. During the night there was profuse sweating, and the abdomen and back became quite painful. On the morning of admission, eating had been impossible on account of soreness of the jaws and neck muscles.

Examination showed a well nourished and developed boy apparently quite ill. The temperature was 103° F., the pulse 120, and the respirations 36. He lay supine by preference, active or passive movement causing pain in the neck, back and abdomen. There was brawny non-pitting edema of the face and eyelids, of the legs and to a slight degree of the trunk. The skin over these areas was smooth and shiny. The face and upper thorax presented a diffuse, dusky red erythema which blanched on pressure; there was slight, much paler redness of the legs below the knees. The muscles of the neck, lumbar region, abdomen and legs were firm and quite tender on pressure.

The head was of normal conformation, the hair abundant and of good texture. There was a healing scalp wound over the right temporo-parietal region which presented no evidence of infection. The ears were negative. The eyelids were moderately edematous and the palpebral conjunctivae deeply injected. The left eye showed marked internal strabismus with limitation of outward rotation; ocular movements otherwise were well performed and not painful. The pupils were round, equal and reacted to light and accommodation. Ophthalmoscopic examination after dilation of the pupils showed nothing remarkable. There was no tenderness over the paranasal sinuses; there was a slight mucoid nasal discharge. The teeth were well preserved. The tongue was coated and a little tremulous. The tonsils were moderately large, red, free from exudate. The entire pharynx was diffusely reddened.

The neck looked normal, there was pain on movement but no rigidity. The thyroid was normal. The anterior cervical, epitrochlear and inguinal lymph nodes were large, soft, insensitive. The thorax was symmetrical and moved well. The lungs were negative throughout. The heart was normal in size and position, no thrills or shocks were noted. The first heart sound was of poor quality at all valve areas and systolic murmurs were heard at the mitral and pulmonic. There was no accentuation of the pulmonic second sound. The heart rate was 120, the rhythm normal, blood pressure 100 systolic, 70 diastolic. The abdomen was flat and showed general limitation of respiratory movement. The walls were held rigidly and there was general tenderness of the muscles. No other evidences of peritoneal irritation were noted. The liver, spleen and kidneys were not felt. The genitalia were normal. The extremities were negative except for the firm edema of the legs which extended from the ankles to the mid-thighs and the rigidity and tenderness of the underlying musculature. There was no evidence of arthritis. The superficial and deep reflexes were all present and seemed normally active.

Examination of the blood showed 5,000,000 erythrocytes and 17,000 leukocytes per cubic millimeter, hemoglobin 85 per cent. A smear showed no morphological abnormalities of the red cells, and no malarial parasites were seen. A differential leukocyte count showed 52 per cent polymorphonuclear neutrophiles, 38 per cent eosinophiles, 5 per cent lymphocytes, 5 per cent monocytes. The blood sugar was 98 mg. per cent, the non-protein-nitrogen 26 mg. per cent. The Wassermann and Kahn tests were negative. The urine contained a trace of albumin and a few granular casts. The phenolsulphonephthalein output was 45 per cent in one hour after intravenous injection. The stools were negative for cysts, ova and parasites; neither blood nor pus was present. The sputum showed no blood nor tubercle bacilli.

The admission diagnosis based on the presence of fever, edema, muscular soreness and eosinophilia was trichinosis. On account of the erythematous rash and red throat, mild scarlet fever was considered a possibility. The temperature fell rapidly, reaching normal on the second day and remaining normal after the third. The eruption faded on the second day leaving a faint brown stain. No desquamation occurred. Edema resolved more gradually persisting until the fifth day. The cardiac bruits were not noted after fever ended although the heart rate remained between 88 and 100 during the entire period of hospitalization. Moderate muscular soreness and stiffness were present for some three weeks and the muscles of the thighs and legs felt firm. No change could be detected in the muscles of the neck and trunk. During the third and fourth weeks of observation the skin of the legs became increasingly tough and inelastic with definite loss of mobility. Repeated examinations of the blood showed persistent leukocytosis and eosinophilia. (See table.) Frequent search of the stools failed to discover parasites of any sort.

On January 3, 1933 a fragment of the right gastrocnemius muscle was removed for histological examination. The wound which had been closed by deep and superficial suture showed infection on the fifth day. *Staphylococcus albus* was recovered

TABLE I

Date	W.B.C.	P.M.N.	Eos.	Lymph.	Mon.
Dec. 16	17,000	52%	38%	5%	5%
Dec. 22	20,000	54%	26%	19%	1%
Dec. 26	21,000	30%	60%	10%	0
Jan. 3	12,250	66%	10%	22%	2%
Jan. 19	12,800	47%	40%	12%	1%

from the pus, and final healing delayed until the fourteenth day. Microscopical examination of the excised muscle showed marked edema with irregularly distributed degeneration of the muscle fibers some of which were fragmented, others hyaline, still others in a state of granular degeneration. There were focal areas of lymphocytic and polymorphonuclear infiltration many of which were interstitial, while others were around the arterioles. There were few if any eosinophiles in these areas of infiltration and no giant cells. No evidence of proliferation of muscle or connective tissue was seen. The walls of some of the arterioles were unduly thick but without evidence of medial or intimal proliferation. No larvae of *Trichinella spiralis* were found. The histological diagnosis was acute to subacute non-suppurative myositis.

The patient was dismissed on January 20, 1933. At this time very little muscular soreness or tenderness remained. The skin of the legs was glossy, firm and inelastic. There was definite diminution in the size of the gastrocnemius muscles of both legs and these as well as the quadriceps and hamstring groups were much firmer than normal. No contractures were present and there was little loss of function. The knee and ankle jerks on both sides were diminished. The boy was seen again five months after dismissal. There was no pain nor tenderness of the leg muscles but slight atrophy of the gastrocnemei was evident. The muscles of the thighs and legs remained firmer than normal, but function was excellent. The skin had resumed a normal appearance but remained inelastic and immobile.

The case is recorded as one of dermatomyositis with an acute and benign course which gives every evidence of early complete recovery. The clinical resemblance to trichinosis was at the onset remarkable. No cause was found for the extreme eosinophilia.

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CONGENITAL OSTEOSCLEROSIS (MARBLE BONE) *

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SINCE Albers-Schönberg [1] first wrote about this rare and interesting condition in 1904, descriptions of it with reports of approximately 30 cases have appeared in the literature. The majority of them originated in Germany with a few from America, Switzerland, France and Italy. Since most of the diagnoses have been made by accident while looking for other conditions, it is probable that it is not so rare as has been believed. Liévre [2] reminds us that it is not likely that the condition would in reality be so largely limited to the German speaking countries and suggests that the diagnosis has doubtless often been missed because of confusion with such other conditions as osteopsathyrosis, rickets, osteomalacia and Recklinghausen's disease. It must be remembered that our knowledge of this disease has been acquired only since the development of the roentgen-ray.

No one has yet offered a satisfactory explanation of the causation of congenital osteosclerosis. Péhu, Policard and Dufourt [3] point out its apparent preference for the Anglo-Saxon race. Kudrjawtzewa [4] believes it is a mutation of the germ plasma which is inherited as a recessive characteristic and which manifests itself through inbreeding. A few cases have been reported in the offspring of blood relatives. Karshner [5] feels that it is a primary dyscrasia of the mesenchyme resulting in abnormal and excessive bone formation. The frequently irregular distribution of the bone density leads Pirie [7] to suggest that the condition is due to a widespread infection beginning at the epiphyseal line and later spreading to the whole medulla. Since the giving of excessive amounts of irradiated ergosterol has produced in animals a hypercalcification, similar in some ways to this condition, the suggestion has been made more than once that an improper vitamin balance might be responsible. It has not been possible to connect the condition with syphilis or any known pathologic condition of the endocrine glands. So, for the present, we must be content with the statement that it is a hereditary, familial and constitutional disease of unknown etiology which may begin in utero.

The pathology consists primarily of a disturbance of ossification consisting of an increase in the hard cortical bone to perhaps twice its normal thickness. The growth takes place from the endosteum entirely with a crowding of the marrow cavity, often with entire obliteration of this and of the spongiosa or with its replacement by fibrous tissue. The epiphyseal lines may show some irregularity with several transverse striations. Autopsy specimens of the bones are hard like ivory, but brittle, and may show old fractures. The marrow cavity may have disappeared. The upper ends of the humeri and lower ends of the femora show the greatest changes.

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Sometimes the sternum, ribs, scapulae and spinal column do not seem to be involved but the changes are usually more or less general including the short bones and those of the skull. Enlargement of the posterior clinoid processes seems to be particularly striking, and necrotic lesions of the alveolar border of the lower jaw have frequently been present. Schinz [8] describes the microscopic picture thus: Cortex thickened; osteoblasts increased in every field; Haversian canals increased in number and ramifications; marrow spaces filled with fibrous tissue; Haversian canals and Howship's lacunae filled with numerous polynuclear osteoclasts. All these indicate an increased resorption of bone followed by a still more marked formation of it.

While the condition appears to be congenital, symptoms may not appear until later in life. Nearly all cases in young persons are underdeveloped physically. The long bones eventually attain their normal length if the individual lives, but the mature figure is generally slender and frail. Walking and talking are late in appearance and hydrocephalus with a retarded mentality is common. The type of facial expression is fairly characteristic. The features are broad, the eyes wide apart, the root of the nose sunken with the tip broad and turned up, the nares being round and far apart. The lips are thick and the hair abundant. The cranial bosses are prominent. Nystagmus is often seen and later optic atrophy and blindness due to the bony structures pressing upon the optic nerve as it passes through the foramen. The skin may be wrinkled and present a senile appearance. It seems that the bones utilize large amounts of calcium at the expense of the teeth; these are always late in eruption and tend to drop out or decay early. Suppuration and necrosis of the lower jaw has been the cause of death in several of the reported cases. Healing of the numerous fractures may be delayed resulting in deformities. These fractures occur from slight trauma, especially in older persons. Coxa vara, coxa valga, scoliosis, beaded ribs, deformed chests and epiphyseal enlargements are fairly common. An anemia, which varies in degree from mild to very severe, is common, and the blood picture sometimes simulates leukemia. The superficial lymph nodes are usually palpable, the liver is generally enlarged and the spleen is apt to be enormously enlarged and very hard.

The most outstanding characteristics are brought out by the roentgen-ray. The skeleton presents an almost uniform opacity, the bones transmitting no rays and appearing on the plate as structureless silhouettes. If seen at all, the medullary cavity is much reduced in size. The picture may look like one of incomplete exposure. The opacity may be more dense in the spine, pelvis, base of the cranium, upper femur and tibia. While the outlines of the bones are generally regular, local thickening may be observed especially along the upper humeri, the lower femora, the ribs, scapulae and posterior clinoid processes. Areas of different density may be seen and transverse bands or striations near the ends of long bones are common. These are seen particularly in the phalanges, metacarpals, metatarsals, fibulae and tibiae. In these same bones and in the ribs are sometimes seen more

or less clearly defined, rounded, or oval opaque islands or spots. There have also been noted, especially in the calcaneum, small, clear areas where the bone is invisible, appearing as holes in the skeleton. Old fractures may be seen and the cartilages appear more calcified than normal.

As has been stated, nearly all cases of this disease are discovered accidentally when roentgen-ray pictures are made of some bone. In early life most of them are diagnosed as rickets and so treated. Syphilis is often suspected and many are given antisyphilitic treatment in spite of a negative Wassermann. In older patients the condition is generally discovered on account of fractures from slight trauma. The striking opacity of the skeleton showing the structureless, silhouette-like shadow is characteristic.

Congenital osteosclerosis can be rapidly fatal, and it is probable that many cases die in utero and others shortly after birth. In those that survive, the condition becomes chronic and it sometimes seems to become arrested. The outcome depends largely upon the development of secondary manifestations such as anemia and hydrocephalus. The fractures finally heal, hydrocephalus causes its usual symptoms, and optic atrophy leads to blindness. A leukemic picture seems to give a bad prognosis.

There is no cure. Careful oral hygiene should be carried out since necrosis of the jaw has terminated many cases. Calcium, phosphorus, cod liver oil, irradiated ergosterol or any other substance that promotes the growth of bone should be avoided. Iron may help the anemia. Persons with the condition should not bear children.

Case Report

W. S. K., male, three and one-half years old, came in because of blindness, enlargement of the head and inability to walk.

History. Father living and well, 26 years of age. Mother living and well, about the same age. She had one ovary, a Fallopian tube and the appendix removed after being married about five months. While she was pregnant with this child and during a later pregnancy she had a great deal of trouble with her teeth—all the fillings came out. She had a Caesarian operation when the patient was two and one-half years old. The baby thus delivered was said to be normal in appearance but died about four hours after delivery from atelectasis. There is no history of any known relatives having a condition similar to that of the patient. The father's blood Wassermann was negative and the mother's was reported to have been 2 plus at one time. The mother had a great deal of nausea and vomiting preceding the birth of the patient and almost miscarried several times. She was given some kind of intravenous medication for this. The mother thought the child was born about two weeks prematurely. There was a prolonged, dry labor but no instruments were used. The baby was blue and difficult to revive. Weight, 8½ pounds. A moderate degree of icterus developed and lasted for a few days. Breast-feeding was carried out for five months but the infant did poorly until weaned. Cod liver oil and orange juice were begun at three months. At this time the spleen was known to be enlarged. At six months it was noticed that the eyesight was poor and that the eyes rolled more or less constantly. At five months the two lower central incisors came through and soon afterwards the two upper central incisors. No other teeth have erupted but the gums have become swollen several times, and were once lanced by a physician. At six or seven months

the child could sit upright and soon learned to scoot along on the floor. He has never walked except when supported or with the aid of braces. He began to talk at an early age and has been very alert mentally, with an unusually good memory and a good vocabulary. A prolonged attack of whooping cough occurred at two years. At two and one-half years he was quite ill with a high fever for about two weeks and was said to have "congested lungs" and an "abscessed spleen." He had a course of ultra-violet ray treatments at about five months with some roentgen-ray exposures over the spleen and some intramuscular antisyphilitic treatments afterwards. Another course of ultra-violet ray treatments was given at 18 months. Cod liver oil and viosterol have been used persistently. The appetite has been generally good and he has had a satisfactory variety of food. He has always slept fairly well except when the intracranial pressure seemed increased. There has been good control of the bladder. The patient has usually shown a feeling of well being and a cheerful disposition.

Examination. Weight, 28.5 pounds. The head appeared large and the fontanelles were closed, but there appeared to be some separation of the sutures. The bosses were very prominent. There was no vision except for the ability to distinguish light from dark. The pupils reacted fairly well to light. The skin and mucous membranes were very pale. There was a marked condition of genu valgum with a great deal of curving of the tibiae. The spleen was enormously enlarged and very hard. The liver was enlarged to a lesser extent. The abdomen was large and of irregular contour due to the large spleen and liver. There were only four teeth (two upper and two lower incisors). The general musculature was very flabby. Both optic nerves showed almost complete atrophy. No disturbance of the general nerve reflexes was noted.

Laboratory. Blood: Hemoglobin 60 per cent. Total erythrocytes 2,620,000. Total leukocytes 14,000. Neutrophiles 38 per cent, lymphocytes 60 per cent, eosinophiles 1 per cent, basophiles 1 per cent. Anisocytosis, poikilocytosis and polychromatophilia were noted. Wassermann and Kline tests were negative. Blood calcium 14.4 mg., phosphates 5.4 mg. Spinal fluid: withdrawn under greatly increased pressure, cell count 2, Wassermann and Kline tests negative, colloidal gold curve 2100000000. The urine was negative except for a very low specific gravity. Roentgen-ray showed marked density of bones all over the body, an increased thickness of the cortex with little or no medullary space—typical of marble bone.

Course. The patient lived about 15 months after the first examination. His condition changed little. During part of this time he had purpuric spots over his body and there was some difficulty with bleeding from the gums. Death was due to an accidental fall with possible intracranial hemorrhage. No autopsy was permitted.

Comment

This case presented most of the characteristics which are typical of the disease. Symptoms showed up sufficiently early to make it seem possible that the condition was present at birth. The difficulty of diagnosis is well illustrated. He was seen early by competent physicians and was treated for rickets and syphilis. We accidentally diagnosed the case by having a roentgen-ray picture made while looking for some other condition. It is not at all improbable that the later baby, that was delivered by Caesarian section and that lived only a few hours, had the same condition. The patient got along quite well considering the fact that there was almost no bone marrow space visible in the pictures and that there was consequently a marked anemia. One must conclude that the great enlargement of the liver

FIG. 1

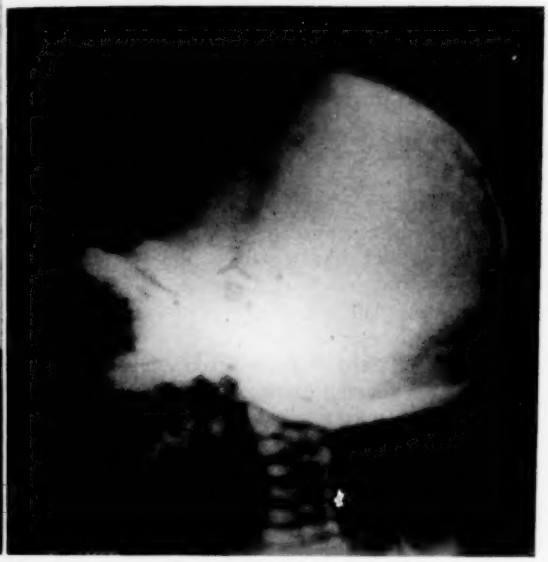

FIG. 2

FIG. 1. Patient 4 years of age, showing characteristic features, large head, eyes widely separated, sunken nose with broad tip. Markings show moderately enlarged liver and enormously enlarged spleen. Marked genu valgum.

FIG. 2. Roentgen-ray of skull. Brings out the marked density of the bones.

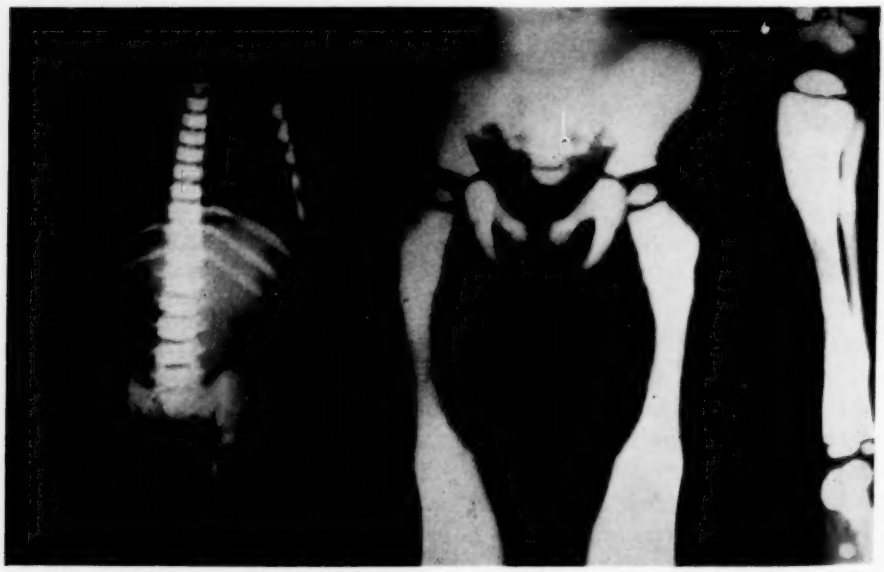

FIG. 3

FIG. 4

FIG. 3. Roentgen-ray of spine showing marked density.

FIG. 4. Roentgen-ray of pelvis, femora, one tibia and fibula, showing the structureless opacity of these bones and the localized thickenings over lower ends of femora.

and spleen must to some extent be due to the resumption by these organs of their hematopoietic functions, in order to compensate for the loss of bone marrow.

Summary

Congenital osteosclerosis or marble is a rare condition but probably occurs more frequently than is generally believed. The cases that are correctly diagnosed are usually discovered more or less accidentally while looking for other conditions. In early life most of them are treated at some time or other for rickets and syphilis. The diagnosis is easily made by taking x-ray pictures of the bones. There is no satisfactory treatment, but the condition sometimes seems to become arrested. The outcome depends largely upon such secondary symptoms as anemia and hydrocephalus. A case report is presented.

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CATHARSIS IN ACUTE UPPER RESPIRATORY INFECTIONS *

By Fred N. Miller, M.D., *Eugene, Oregon*

Since the various factors involved in the etiology of the common cold and of grippal infections are at best imperfectly understood, it is not surprising that the therapeutic management of acute upper respiratory disorders has not been satisfactorily established. Present treatment is largely a mélange of traditional procedures which are varied from time to time usually only in minor details. The evaluation of any therapeutic procedure or agent in the treatment of these infections is especially difficult for two reasons. In the first place there is a considerable variation in the manifestations of respiratory infections not only from season to season but from month to month. Anyone who has a considerable practice with this type of affection soon is impressed with the fact that the virulence measured either by the extent of the prostration or the number of complications varies tremendously in any community sometimes in one or two weeks. A second difficulty in the proper evaluation of a therapeutic remedy or procedure in the upper-respiratory infections is due to the fact that such infections as a rule run a relatively short course and tend to clear up spontaneously. Nevertheless because of the great prevalence of these infections and the resultant morbidity and economic loss, and because of the complications and sequelae which are so frequently serious, it is important to analyze in as critical a manner as possible the management of these infections.

One of the most common practices of physicians, in the past at least, has been to administer a cathartic either at the onset of a cold or soon thereafter. The importance of "keeping the bowels open" is practically always stressed in the advice given to the laymen and is not infrequently advocated in textbooks of medicine and in current medical literature. Because of the frequency with which a cathartic is prescribed or administered for a cold, and because of the importance of a proper evaluation of the treatment of acute upper respiratory infections, it seemed desirable to attempt to get some evidence as to the value of catharsis in these conditions.

Infirmary or bed patients were chosen because of the possibility for control. Previous experience with ambulatory university students had demonstrated the practical difficulty of having them return for observation or the even greater difficulty of assuring their following directions. Infirmary patients are under strict control and it was therefore considered that the alternate case method might satisfactorily be applied to these patients.

Cases were chosen in which the nose, throat, trachea and upper bronchi were affected and in whom there was no demonstrable complication nor any gastrointestinal disturbance and a relatively few cases were chosen each

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From the Student Health Service, University of Oregon.

year since 1927, to allow for seasonal variation in virulence. Cases chosen for this study were put on "routine upper respiratory orders" and the Infirmary nurses were instructed to have all such cases fill out the following questionnaire:

QUESTIONNAIRE FOR STUDENTS WITH COLDS

Please fill out questionnaire carefully. Colds in the head and chest are very common among students and we are anxious to study the results of our treatment carefully so that we can treat these conditions in the best possible way.

1. How many days have you had a cold or been sick?
2. Do you feel sick all over?
3. Does your head ache?
4. Are you tired or all worn out?
5. Did your bowels move today? Yesterday?
6. Have your bowels been moving as well as usual during the past week?
7. Have you taken a cathartic in the last three or four days?
8. Do you usually take a cathartic for severe colds? If so, are you strongly of the opinion that it helps you?

Roughly one-third of the cases had already taken a cathartic before presenting themselves to a doctor at the Health Service. The alternate cases of those who had not previously taken a cathartic were then given one ounce of magnesium sulphate (a few students refused and a few others were missed by the nurses). Other treatment was largely symptomatic—salicylates for malaise, ephedrine for the nose, Dobell's gargle, steam inhalations and codeine for cough were commonly employed but always without any knowledge on the part of the prescribing physician as to whether or not the patient had received a cathartic. At the end of the experimental period (1927 to 1934) the cases were divided into three groups and the results are tabulated in table 1.

TABLE I

	No.	Average Max. Temp.	Average Hosp. Days
Students who had taken a cathartic previous to admission	88	100.17	4.12
Students who were given 1 oz. of magnesium sulphate	70	100.12	4.36
Students who were given no cathartic	99	100.05	4.12

It is felt that both the maximum temperature and the number of hospital days are at least fairly objective criteria and therefore are proper measures of the effect of catharsis since catharsis was produced in 69 of the 70 (98.5 per cent) given magnesium sulphate.

It is interesting to note that 102 (40 per cent) of the 257 state they usually take a cathartic for a severe cold but only 84 are strongly of the opinion that a cathartic really helps them. It is possible that the percentage of the general population that takes a cathartic for a severe cold is even greater than the 40 per cent found in this group.

CONCLUSION

Catharsis taken early or at the time of admission to a university Health Service Infirmary had no effect in acute upper respiratory infections as measured by the maximum temperature or the hospitalization time.

EDITORIAL

*HOW SEX AFFECTS THE INCIDENCE OF DISEASE AND MORTALITY**

ALMOST everyone who reports any considerable number of cases representative of a certain disease mentions the incidence by sex. When significant differences exist, and when an explanation is attempted, it is almost invariably based on extraneous or environmental factors. Following this general plan pregnancy and obesity are said to cause the greater incidence of diseases of the gall-bladder among females, and alcoholism explains the predominance of males among those who have hepatic cirrhosis; the ratio of males to females in these two conditions, however, is about the same whether one is considering children or adults. It is apparent, therefore, that obesity, pregnancy, and alcoholism are not the factors responsible for the interesting incidence of these diseases by sex.

A study has been made of the incidence by sex in approximately 300,000 cases of disease affecting structures which have tissues and functions common to both sexes.[1] All of the diseases of the digestive tract that were studied affected males predominantly, except cholelithiasis, cancer of the gall-bladder, carcinoid tumor of the appendix, and gastric ulcer. Of the diseases of the respiratory tract and upper part of the digestive tract, only pulmonary tuberculosis of children affects females more frequently than males. Cancer of the lip, larynx, tongue, tonsils, bronchi, and pharynx, and pneumonia, actinomycosis, asthma, and bronchiectasis are predominantly diseases of males. Degenerative and inflammatory diseases of the arteries, and blood dyscrasias such as leukemia, pernicious and splenic anemia, and polycythemia affect males more often than females. Syphilis of the heart, meninges, skin and mucous membranes, and of the central nervous system much more frequently follows primary infection of males than of females. Of diseases of the bones, joints, and urinary tract, only chronic infectious arthritis affects females more commonly than males, whereas gout, malignancy of the bladder, kidney, and bones, osteomyelitis, renal tuberculosis, glomerular nephritis, renal stone, and tuberculous arthritis affect males predominantly.

A reversal of the incidence of diseases by sex is noted in functional disturbances such as Raynaud's disease, migraine, hysteria, chronic nervous exhaustion and biologic inferiority, by which conditions females are more commonly affected than males. Data show that four men commit suicide to each woman, although women make more suicidal " attempts " than men.

These studies in morbidity indicate that males are less favorably situated as far as serious organic disease is concerned. This fact should influence comparative expectancies of life and the percentage distribution of males and females in the entire population. Figures for 1927 reveal that, at the age

* Submitted for publication January 3, 1935.

[1] ALLEN, E. V.: The relationship of sex to disease, ANN. INT. MED., 1934, vii, 1000–1012.

of 10 years, girls could expect 55.32 years of life and boys only 51.88 years. The 1920 census figures for the registration area of the United States show that, after the age of 55 years, there is a gradually diminishing predominance of males in the population until, at the age of 75 years, the women outnumber the men and continue to do so in the more advanced ages. Of the centenarians in the United States in 1920, almost twice as many were women as men.

The factors which are usually set down in explanation of the greater incidence of organic disease and mortality among males are overwork, alcoholism, venery, tobaccoism, exposure to the elements, industrial hazards, and irregular habits of eating and drinking. The validity of these banal theories may be tested in two series of observations regarding the influence of sex on mortality, in both of which extraneous factors are entirely common to both sexes and, therefore, negligible:

In the registration area of the United States in 1920, 8,500 males and 6,700 females died for each 100,000 males and for each 100,000 females, respectively, of that part of the total population which was less than one year of age. Similar predominant mortality existed for males of all ages less than 20 years. This condition was likewise true in the census years 1900, 1910, and 1930. It would be difficult logically to attribute the greater susceptibility of infant and adolescent males to fatal disease to extraneous factors, as they appear to be exposed to about the same environment as females of similar age. An even better control is the intra-uterine period of life. The mortality rates for males during intra-uterine life is consistently higher, varying with the different months after conception from 375 to 118 males for each 100 females.

Further inquiry into the effect of habits and environment on differential sex mortality is aided by observations relative to animals.[2] Studies of fish reveal that, as a result of the greater incidence of death among males, there is an increase in the ratio of the number of females to the number of the males as the age of the fish increases. If both sexes of swordtail minnows of equal age are subjected to deleterious solutions, such as potassium cyanide and alcohol, the males invariably succumb first. Conclusions of a similar nature apply to meal-worm beetles, fruit flies, decapods, schizapods, amphipods, spiders, insects and copepods. The observations regarding the last mentioned are amusing. The males are dwarfs which attach themselves to females of their own age and litter and cling to them all their lives. Even this parasitic existence does not protect the male from death at a comparative youthful age.

Two conclusions from such data are inevitable: *the male of both animals and humans is inferior in constitutional vigor and vitality, and this inferiority is internal and constitutional and not external or adventitious.*

[2] ALLEN, E. V.: The difference in mortality of animals by sexes, Proc. Staff Meet. Mayo Clinic, 1933, viii, 755–757.

The cause of the inferiority of the male is far from apparent. The theory that the usual unmatched chromosome of males is etiologic is refuted by evidence that certain species of females with an unmatched chromosome are superior to males.

The apparent higher metabolism of males, as exemplified by the sperm which is small, active, and energy-expending in contrast to the ovum which is large, quiescent, and energy-storing, is a far from satisfactory explanation. Inscrutability relative to cause exists now, and we suspect, will continue to exist. This state need not detract from the fact that sex-linked inferiority of the male is incontrovertible. *There seems no doubt that, speaking comparatively, the price of maleness is weakness.*

E. V. A.

REVIEWS

Atlas Fundus Oculi. By WILLIAM HOLLAND WILMER, M.D., LL.D., Sc.D., Professor of Ophthalmology of Johns Hopkins University and Director of the Wilmer Institute; with an introduction by Warfield T. Longcope, M.D. 22.5 × 28.5 cm. The Macmillan Company, New York. 1934. Price, $35.00.

This volume includes 100 colored plates of normal variations and pathological conditions of the fundus oculi as seen by the author in his extensive and varied experience.

In the introduction Dr. Longcope points out the value of the ophthalmoscope to the internist in that the finer vessels can be studied which is a great aid in the differential diagnosis of various vascular diseases as well as a help in diagnosing blood and kidney conditions, suppurative processes, etc.

The author describes in detail the method of using the ophthalmoscope and the various points to be studied. He points out the normal variations that may be found in the color of the fundi of different races, also the variations in the color of the nerve head with its physiological cup.

The main portion of the work consists of the 100 colored plates which are accurately reproduced in color from original colored drawings made of the patient by the staff artist of the Wilmer Institute, Mrs. Annette Burgess. Opposite each plate is a brief description of the case giving the history with both laboratory and ophthalmological findings and its diagnosis. In several instances a plate is shown of a case at the inception of the condition and another plate of the same case after treatment had been inaugurated.

While other excellent atlases of the fundi oculi have been published, especially that of Frost, none have attained the perfection in reproduction or shown the great variety of lesions that the present atlas presents.

The author, the artist, the engravers and the publishers should all be congratulated upon this superb work which undoubtedly will remain as a standard for many years. Every oculist and every internist who is constantly making differential diagnoses should have this volume for reference when studying the fundus oculi.

C. A. C.

Cataract: Its Etiology and Treatment. By C. A. CLAPP, M.D., F.A.C.S., Professor of Ophthalmology University of Maryland, Associate Professor of Ophthalmology Johns Hopkins University; Foreword by Dr. William H. Wilmer. 254 pages. Lea and Febiger, Philadelphia. 1934. Price, $4.00.

Since cataract is one of the most frequent causes of poor vision in the old and not infrequently in the younger patient, its etiology, prevention, and treatment are of vital interest to every ophthalmologist and internist. This volume, "Cataract, Etiology and Treatment" is, it would seem, the rare combination of a wealth of facts in comprehensive form, collected into the smallest space feasible. It contains in addition to what the title implies, chapters on the development, comparative anatomy, anatomy, nourishment and growth, physiology and chemistry of the normal lens, and congenital anomalies of the lens other than cataract. The chapters on the development of the lens and the comparative anatomy of the lens were written by Ida Mann of London.

Some of the more practically inclined may criticize certain portions, chiefly the chapter on the chemistry of the lens, and portions of the chapter on etiology, as being too scientific for a volume of this nature, but the patience of these will be amply rewarded by the very practical and thorough discussion of treatment.

As seen from the size of the bibliography, a vast amount of literature has been covered in the preparation of this monograph. The ideas and theories of various workers, often conflicting, are clearly presented, and these should serve as a stimulus to further research. Those students particularly interested in the chemistry and physiology of the lens will find facts of interest to them.

The volume should appeal to the investigator, the practitioner of ophthalmology and the internist who wish a compact work on the crystalline lens.

H. F. G.

Periodic Fertility and Sterility in Woman—A Natural Method of Birth Control. By Professor HERMANN KNAUS, Head of the Clinic for Gynecology and Obstetrics of the German University of Prague; Foreword by Professor F. H. A. MARSHALL, F.R.S., Cambridge, England. Authorized English Translation by D. H. KITCHIN and KATHLEEN KITCHIN, M.Sc., M.B., B.S., London. 162 pages; 17.5 × 24.5 cm.; 64 illustrations and 12 tables. Wilhelm Maudrich, Vienna (book obtainable in U. S. A. and Canada through the Concip Company, Hobart, Indiana). 1934. Price, $6.00.

Both physicians and laymen are now giving much thought to the so-called "safe period," and the subject is being so universally discussed that this translation of Professor Knaus' comprehensive book on "Periodic Fertility and Sterility in Woman" should be read with interest by great numbers of English-speaking people.

Dr. Knaus started his study of the physiology and pharmacology of the uterine muscle in 1924, and in 1927 he discovered a reaction of the uterine musculature by means of which the exact day of ovulation can be determined. Through this investigation and through studies on the viability of the human ovum and spermatazoa, Dr. Knaus concludes that in women with regularly recurring menstrual periods conception can occur during only five days of a menstrual cycle. However, in order properly to determine the days on which conception can occur it is necessary for a woman to keep a very exact record of the days of onset of several successive menstrual periods. The author emphasizes that those women who do not menstruate at regular intervals must be considered to be fertile for more than five days of the cycle. Nevertheless, he feels that it is possible to determine the period of fertility and sterility in practically all women.

Some gynecologists do not believe that this method of birth control is as infallible as it is stated to be in this book, but it must be remembered by all critics that no other method is absolutely certain. Dr. Knaus claims that the few reported failures that have followed the use of this method of birth control have all been due to women not keeping exact records of their menstrual cycles.

This book has been interestingly written and well translated into English. The author makes of his subject an almost continuous story which holds the reader's interest throughout the entire 148 pages of text. At the back of the book are 14 pages of bibliography which include practically all the important articles which have been written on this subject. Not only the gynecologists and the physiologists should become fairly familiar with Dr. Knaus' work but also the general practitioner, for it is to the latter that women usually go to make inquiries about the safe period.

L. B.

Conception Period of Women. By KYUSAKU OGINO, M.D., Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan. 94 pages; 12.5 × 19 cm. Medical Arts Publishing Co., Harrisburg, Pennsylvania. 1934. Price, $1.00.

This booklet, written by a Japanese gynecologist, has received considerable publicity throughout the United States. The last 10 pages are a reprint of an article

by three American physicians, A. G. Miller, C. H. Schultz and D. W. Anderson, which appeared in the June 1933 issue of *Surgery, Gynecology and Obstetrics*. This article essentially covers all the points presented by Dr. Ogino.

It is obvious that Ogino has formed his conclusions from a very small number of cases, and that although his arguments are very logical he has not ruled out entirely the possibilities of error. Nevertheless, his conclusions are interesting and his diagrams are well got up.

He states that "the period of ovulation . . . is . . . from the twelfth to the sixteenth day before the subsequent menstruation, having no connection with the length of menses. . . . The human conception period is in the eight days from the twelfth to the nineteenth day before the subsequent menstruation." He gives as the formula for calculating the conception period:

The first day of the conception period = 10 plus the number of days of the minimal cycle — 28.

The last day of the conception period = 17 plus the number of days of the maximal cycle — 28."

The final conclusion, therefore, is that if coitus is indulged in outside of the conception time there is no danger of pregnancy.

J. L. McC.

The Heart Visible. By J. Polevski, M.D., Attending Physician and Cardiologist, Newark Beth Israel Hospital. 207 pages; 16 × 23.5 cm. F. A. Davis Co., Philadelphia. 1934. Price, $5.00.

This volume deals with the roentgenologic study of the heart. It is divided into six parts: General Considerations, Methods of Roentgenologic Study, The Normal Heart, The Abnormal Heart, The Pericardium, The Great Vessels. It contains 122 diagrams and reproductions of films. These are, on the whole, excellent. The author points out the futility of depending upon a single antero-posterior view of the heart for the purpose of roentgenologic study and diagnosis, and of depending upon simple transverse measurements of the heart in arriving at a decision as to the normality of the heart. Complete fluoroscopic examination is stressed. Some information in regard to the history of the patient and the ability to use a stethoscope is advocated for the roentgenologist in order for him to be of the greatest possible help in arriving at a diagnosis. This volume is recommended to cardiologists and roentgenologists and all others interested in the subject.

W. S. L., Jr.

Body Mechanics in the Study and Treatment of Disease. By Joel E. Goldthwait, M.D., LL.D. 281 pages; 14 × 20.5 cm. J. B. Lippincott Co., Philadelphia. 1934. Price, $5.00.

In the preface the author offers a just criticism of the whole medical profession, to wit, that the profession does not give the chronic patient a fair "break"; so much attention is paid to the causes, diagnosis, and treatment of the acutely ill patient that the one who does not respond promptly is slowly pushed aside and preferably forgotten. Poor bodily mechanics will certainly play a far greater rôle in the chronic patient than in the acute one, and this factor is quite apparent to those of us who treat chronically ill people. In general also it is a well known fact that improved posture and bodily tone make for better health.

In Chapters 5 to 9 inclusive the author has shown how poor bodily mechanics to a large degree may cause most of the chronic ailments of the individual, even those

which have ordinarily been considered of infectious type. The author's long experience with postural conditions lends weight to his statements on this subject.

The chapters on treatment reveal nothing particularly new to those who have been following the developments in physical therapy, but they do outline a series of exercises, etc., which will certainly improve a patient's general physiological activities and in so doing react favorably on many pathological conditions.

The cases reviewed in the last two chapters lend strength to the theory and proof to the statements made in the earlier chapters. The results obtained are very striking.

The presentation of the subject loses some of its force because of a certain vagueness in the author's phraseology. The book as a whole, however, will convince most physicians that in the treatment of the chronic patient a sane and intelligent application of the methods of physical therapy is a very valuable adjunct to other forms of treatment.

A. F. V.

COLLEGE NEWS NOTES

New Life Members of the College

The College is gratified to announce that the following Fellows have become Life Members by contributing the specified fees for their respective ages to the Endowment Fund:

Dr. Ralph O. Clock, New York, N. Y.	January 1, 1935
Dr. Charles F. Morsman, Hot Springs, S. D.	" 1, 1935
Dr. Lawrason Brown, Saranac Lake, N. Y.	" 11, 1935
Dr. Grant O. Favorite, Philadelphia, Pa.	" 11, 1935
Dr. James Alex. Miller, New York, N. Y.	" 12, 1935
Dr. Edward C. Klein, Jr., Newark, N. J.	" 14, 1935

Some years ago the Board of Regents, believing a sound financial foundation to be one of the best guarantees of insuring the stability and perpetuity of the American College of Physicians, provided for the building up of an Endowment Fund, "the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income shall be available for carrying out the purposes of the organization."

The Endowment Fund had reached a total of $55,640.00 on December 31, 1934, income from which has materially helped in carrying on the work of the College during the recent years. Especially has the income contributed toward special activities of the College, such as the stimulation of research through the awards of the Phillips Memorial Prize and the Research Fellowship of the College, established during the past year.

Until 1933, the Life Membership fee amounted to $500.00. A careful study, from an actuarial standpoint, led the Board of Regents to adopt a new plan during the early part of 1933 by which a Fellow or Master may be accorded Life Membership up to 45 years of age by the payment of $300.00 in addition to the Initiation Fee paid at the time of election. From 45 years of age to 58 years of age, a Fellow or Master shall pay an amount equivalent to the total amount of dues he would ordinarily pay from his present age to the age of 65 years. From the age of 58 forward, the minimum Life Membership fee is $100.00, in addition to the original initiation fee.

The Life Membership Fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Clinical Sessions, and to the official publications of the College, including the Directory and the Annals of Internal Medicine. An official Life Membership Certificate is issued to each new Life Member, and his name is engrossed on the permanent scroll of Contributors to the College Endowment Fund.

Quite aside from any personal advantages which Life Membership confers, members who can afford to do so should subscribe for the express purpose of putting the College in position, financially, to broaden its activities along lines which are clearly suggested at this time, when there is so much conflict of thought and opinion on the subjects of medical practice, medical fees, medical education, and other topics which are of primary interest to internists.

The plan is sound financially, both from the standpoint of the College and of the member. It affords the member an opportunity of paying his full dues during his productive years and while his income is largest, thus avoiding the burden of dues later in life. The plan provides a means for underwriting dues years in advance, but of receiving the premium of active membership throughout one's entire life. A member pays no more for Life Membership than he would pay for ordinary active membership to 65 years of age, without active membership thereafter (ordinary

members, upon reaching the age of 65, are entitled to the waiver of their dues for the balance of their lives; but, in effect, they become inactive members, because they do not receive the Journal, the Directory, or other publications, except upon direct subscription). Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life.

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Oliver T. Osborne (Fellow), New Haven, Connecticut—one book, "Mouth Infection."

Dr. Arthur C. Clasen (Fellow), Kansas City, Missouri—two reprints.

Dr. Emil F. Koch (Fellow), Brooklyn, New York—one reprint.

Dr. Lea A. Riely (Fellow), Oklahoma City, Oklahoma—four reprints.

Dr. Robert B. Radl (Fellow), Minneapolis, Minnesota—two reprints.

The 1935 Annual Clinical Congress of the American College of Surgeons will be held in San Francisco, October 28 to November 1.

Dr. George R. Minot (Fellow), Boston, Massachusetts, addressed the Royal Society of Medicine, London, England, November 29, 1934, on "Some Aspects of Anemia," and also addressed the University of Copenhagen, Copenhagen, Denmark, December 6, 1934, on the same subject. Dr. Minot addressed the staff and students of Guy's Hospital, London, during the same visit, on "Pernicious Anemia and the Interpretation of Reticulocyte Responses." On December 12, at the Caroline Institute, Stockholm, Sweden, Dr. Minot delivered a Nobel Lecture on "The Development of Liver Therapy in Pernicious Anemia."

Dr. George Herrmann (Fellow), Galveston, Texas, is Chairman of the Section on Medicine of the Southern Medical Association for the year 1934 to 1935, ending with the meeting of that society in St. Louis, Missouri, during November of this year.

Dr. James Murray Washburn (Fellow), Chicago, retired during the past summer from active practice. Dr. Washburn has founded at Lake Lure, N. C., not far from Asheville, an institution called "The Chalet," which will care for a limited number of men patients who are in need of rest and recuperation.

Dr. J. L. McCartney (Fellow), who has entered the private practice of psychiatry in Portland, has taken charge of a new psychiatric institution in that city known as "The Northwest Retreat," the purpose of which is to care for neurotic individuals who are in need of intensive psychotherapy.

Dr. Leila E. Andrews (Fellow), Oklahoma City, Okla., addressed the Tulsa County Medical Society at Tulsa, Okla., on November 12, 1934. Her subject was "Calcium Deficiency."

Abridged Minutes of the Board of Regents, Philadelphia, Pa., December 16, 1934

The Board of Regents of the American College of Physicians met and was called to order at the College Headquarters, Philadelphia, Pa., at 10:00 a.m., December 16, 1934, by the President, Dr. Jonathan C. Meakins.

Those present were: Dr. Jonathan C. Meakins, Dr. James Alex. Miller, Dr. James H. Means, Dr. William D. Stroud, Dr. Randolph Lyons, Dr. William Gerry Morgan, Dr. David P. Barr, Dr. James B. Herrick, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Walter L. Bierring, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. Luther F. Warren, Dr. Roger I. Lee, Dr. Sydney R. Miller, Dr. George Morris Piersol, Dr. Maurice C. Pincoffs, Dr. Ernest B. Bradley. In addition, there were present Dr. Charles F. Martin, Chairman of the Finance Committee, Dr. Charles G. Jennings, member of the Committee on Public Relations, Dr. Charles H. Cocke, member of the Committee on Credentials, Dr. Alfred Stengel, General Chairman of the forthcoming Philadelphia Clinical Session, and Mr. E. R. Loveland, Executive Secretary.

The Executive Secretary acted as Secretary of the meeting.

An abstract of the Minutes of the meetings of the Board of Regents held during the Chicago Clinical Session was read and approved.

After brief comments by President Meakins, Secretary-General Morgan presented the following communications:

(1) A set of resolutions from the Chicago Roentgen Society dealing with a matter of bringing from foreign countries physicians in different specialties who were said to be displacing competent American physicians in hospital appointments.

On motion by Dr. Bierring, seconded by Dr. Jones, and regularly carried, it was

Resolved, that the communication from the Chicago Roentgen Society be received and filed.

(2) A letter and set of resolutions from the Committee on Health and Public Instruction of the St. Louis Medical Society dealing with the discontinuance of the Reserve Officers' Training Corps Units in medical schools, and petitioning the re-establishment of the Corps as soon as possible.

On motion, seconded and regularly carried, it was

Resolved, that the communication be received and filed.

(3) A letter from Dr. W. A. Stauffer, of Elkhart, Ind., offering to present to the College certain medical books.

Upon motion, seconded and regularly carried, it was

Resolved to thank Dr. Stauffer for his offer to present the books to the American College of Physicians, but to suggest that the books be donated to some other regular medical library, inasmuch as the books in the Library of the American College of Physicians are those of which our own members are the authors.

On individual motions the following resignations were accepted:

Associates

Thomas J. Burrage, Portland, Maine
J. C. Burkle, La Fayette, Ind.
J. Alexander Clarke, Jr., Philadelphia, Pa.
H. H. Heuston, Boulder, Colo.

Fellows

Bartgis McGlone, Philadelphia, Pa.
Giuseppe Vercellini, Los Angeles, Calif.

The Executive Secretary then presented certain communications concerning special cases affecting fees and dues, the cases being acted upon individually by the Board of Regents.

President Meakins announced the names of ten Associates who had been dropped from the roster of the College because their Associateship period of five years had expired without their qualifying for Fellowship.

He announced further the names of ten Fellows and two Associates whose names had been returned to the roster of the College because they had paid up their delinquent dues of two years' standing.

The Executive Secretary reported the receipt of letters of regret at inability to attend this meeting from Drs. Crispin, Churchill, Elliott, Kerr, Pottenger and Richards. He further read a communication from Dr. Dwight O'Hara, of Boston, and from Dr. Frank R. Starkey, of Philadelphia, which required no action.

President Meakins reported the following deaths among Associates and Fellows of the College since the last meeting of the Board of Regents:

Associates

George M. Gilchrist, Groton, N. Y.....August 25, 1934
James L. Junk, Connellsville, Pa.....May 20, 1934
True E. Makepeace, Farmington, Maine.....November 6, 1934
Curran Pope, Louisville, Ky.....September 21, 1934

Fellows

Bailey K. Ashford, San Juan, P. R.....November 1, 1934
Isidor David Bronfin, Denver, Colo.....July 31, 1934
Claude E. Case, Clifton Springs, N. Y.....January 27, 1934
Merchant William Colgin, Waco, Tex.....July 15, 1934
Addison E. Elliott, San Diego, Calif.....April 9, 1934
Benjamin Gutmann, New Brunswick, N. J.....August 7, 1934
G. Walter Holden, Denver, Colo.....July 12, 1934
James Edwin Houghton, Washington, D. C.....May 3, 1934
Morris H. Kahn, New York, N. Y.....July 13, 1934
Hugh Mackay, Winnipeg, Man., Can.....October 12, 1934
Thomas E. Satterthwaite, New York, N. Y.....September 19, 1934
Paul Galpin Shipley, Baltimore, Md.....September 12, 1934
John Peter Zohlen, Sheboygan, Wis.....June 2, 1934

The Executive Secretary then presented the following resignations, which were acted upon as indicated:

Associates

Thomas J. Burrage, Portland, Maine
Upon motion by Dr. Bierring, seconded by Dr. White, and regularly adopted, it was
Resolved, that the resignation of Dr. Thomas J. Burrage be accepted.
J. C. Burkle, La Fayette, Ind.
Upon motion by Dr. Pepper, seconded by Dr. James Alex. Miller, and regularly adopted, it was
Resolved, that the resignation of Dr. J. C. Burkle be accepted.
J. Alexander Clarke, Jr., Philadelphia, Pa.
Upon motion by Dr. White, seconded by Dr. James Alex. Miller, and regularly adopted, it was
Resolved, that the resignation of Dr. J. Alexander Clarke, Jr. be accepted.
H. H. Heuston, Boulder, Colo.
Upon motion, seconded and regularly adopted, it was
Resolved, that the resignation of Dr. H. H. Heuston be accepted.

Fellows

Bartgis McGlone, Philadelphia, Pa.

Upon motion by Dr. White, seconded by Dr. James Alex. Miller, and regularly carried, it was

Resolved, that the resignation of Dr. Bartgis McGlone be accepted.

Dr. George Morris Piersol, Chairman of the Committee on Credentials, reported that his Committee had met on December 15 and had examined the credentials of the candidates for Associateship and Fellowship. Of 73 candidates for Fellowship, the Committee presented to the Board of Regents the names of 58 recommended for election to Fellowship and seven for election to Associateship, instead of Fellowship. Of 109 candidates for Associateship, the Committee presented to the Board of Regents the names of 86 recommended for election to Associateship. (Editor's note: The list of physicians elected to Fellowship and Associateship was published in the January 1935, issue of this journal.)

Chairman Piersol then presented the case of Dr. Paul John Hanzlik, of San Francisco, Calif., who is a full-time teacher. He was elected a year ago subject to the customary reduction in fees and dues, but Dr. Hanzlik had written a letter stating that for financial reasons he could not avail himself of the election if he had to pay an initiation fee, contending that like Dr. Addis he should be granted a waiver of such fee.

Upon motion by Dr. Warren, seconded by Dr. Bierring, and regularly carried, it was

Resolved, that the initiation fee of Dr. Paul John Hanzlik be waived for financial reasons and his dues be reduced to $10.00 per annum.

Chairman Piersol then presented the case of Dr. Neuton S. Stern, of Memphis, Tenn., who was elected a Fellow of the College in 1926, but who had been unable to pay the initiation fee and take up his Fellowship for financial reasons. Dr. Stern had sent his check for $100.00, along with an application.

Upon motion by Dr. Piersol, seconded by Dr. James Alex. Miller, it was

Resolved, that Dr. Neuton S. Stern's application for the reinstatement of his name on the Fellowship Roster be approved as of the present date, and that his initiation fee be accepted.

Chairman Piersol then read a communication from the Executive Secretary concerning the number of candidates that are elected, both to Fellowship and Associateship, but who are slow to take up their election by the payment of the required fees. After general discussion by members of the Board, it was the consensus of opinion that the Executive Secretary should work out a plan with the proposer, possibly by having a statement added to the application form, or enclosed in the letter of acknowledgment of the receipt of applications (under no circumstances with the candidate directly), by which it could be determined in advance that the candidate would promptly take up his election, if recommended by the Committee on Credentials.

Chairman Piersol then read a communication from the Surgeon General of the Army, Dr. Robert U. Patterson, in regard to suggestions for additional or supplementary eligibility requirements for the personnel of the Medical Corps of the U. S. Army when presented for membership in the College. Dr. Patterson, it was evident, was seeking a method of measuring men as the criteria for selection of candidates. After general discussion, on motion by Dr. Piersol, seconded by Dr. Bierring and regularly carried, it was

Resolved, that the Surgeon General of the U. S. Army be requested to get in touch with the Surgeon General of the U. S. Navy, in order to work out some scheme, mutually agreeable, for the further determination of candidates for Associateship and Fellowship from both Services.

It was suggested that this be taken up with the Surgeons General by the Committee on Credentials.

Dr. O. H. Perry Pepper, Chairman of the Committee on Examinations, reported as follows: "This Committee was appointed by President Meakins following the adoption by the Board of Regents, on April 17, 1934, of a report by the Committee on Specialization, that report containing six items (see page 585, Minutes of the Board Regents). The first item stated 'in addition to the present requirements for Associateship those candidates who have been approved by the Committee on Credentials shall be required to pass a written examination in Internal Medicine.' In spite of that action, your Committee on Examinations, after studying the matter and exchanging ideas by mail, have come to the conclusion that it would be impractical for this College to give an examination for admission to Associateship at this time. We do think it would be feasible, perhaps, to give an examination for Fellowship, but we beg to report that the Committee believes that the following premises must be accepted: (1) some improvement in the method of selection of members is desirable; (2) the College should not embark on any examination program if there is any danger of this program having to be abandoned later, either because of the difficulty of carrying it out or because of a falling off in applications; (3) any program for examination must be technically feasible, and not too discouraging to the man, and must be of dignified character; (4) the giving of examinations implies, on present figures, the examination of approximately 200 men a year, scattered throughout every State of this country and in Canada, Panama and elsewhere; (5) there is no reason to think that these examinations would not have to be given with every caution and safeguard that the National Board and College Entrance Examinations require. This includes protection of papers prior to examination, proctoring during examination and proper allowance for differences of time in different geographical areas.

"In view of the difficulties and dangers inherent in the giving of an examination for admission to Associateship, the Committee recommends that for the present it is inadvisable to make the attempt. Every effort, however, should be made to raise the standards for admission and to improve the present machinery to that end, granting that the Board of Regents revokes its action of last spring. In view of our recommendation and agreement to dispense with an examination for Associateship, the College should try to work out a scheme for examining those Associates coming up for Fellowship. This would lead to our having to examine 20 per cent fewer candidates than we would deal with if the examination were for Associateship.

"The Committee believes that an examination for transfer from Associateship to Fellowship is both feasible and desirable, if carried out in the following manner:

"(1) The examination to be held annually at the time and place of the annual meeting of the College.

"(2) That Associates in the third year of their membership shall be eligible to appear for examination for Fellowship if approved by the Committee on Credentials. They must become Fellows within five years after election to Associateship or be dropped.

"(3) That an examination fee of $10.00 be required for taking this examination, which fee would be deducted from the regular initiation fee in the case of successful candidates.

"(4) The examination to be the direct responsibility of a committee of five appointed by the President, the Chairman of which shall be a Regent, one member a member of the Committee on Credentials but whose other members may be selected from the membership at large. It is suggested that Fellows not connected with teaching institutions be represented on this committee.

"(5) The duties of the Committee shall be the control of the examination which should be both written and practical, and the recommendation to the Regents of the successful candidates for advancement to Fellowship.

"(6) The necessary expenditures of the Examination Committee to be authorized by the Regents and included in the Annual Budget.

"(7) Examination for Fellowship shall be required of Associates elected after April 1935.

"(8) The Associates advanced to Fellowship by examination shall have the fact recorded on their Certificate in the words 'Fellowship by Examination.'

"In explanation it may be added that within the five year period the Associate should attend several meetings and that the examination would therefore entail no travel or expense. By limiting the examination to advancement to Fellowship, the number of candidates will be reduced by approximately 20 per cent. By giving but one examination annually and in only one place most of the difficulties of control are avoided.

"Finally, the Committee would point out that in a few years if the examination proves efficient the College might consider the desirability of granting to those who pass this examination or perhaps a second more difficult test, some term such as licentiate, indicating their qualification as a specialist in internal medicine.

"The Committee would point out that:

"(1) The establishment of such an examination will inevitably result in limiting our future membership to those engaged in internal medicine (and pediatrics) and to the exclusion of pathologists, roentgenologists, dermatologists, many of whom are now members.

"(2) The attempt to give a practical examination may prove impractical if the number of candidates at any one examination is large.

"(3) To give a practical examination sufficiently detailed and difficult to make it worth while will entail a great deal of work and time on the part of the Committee—probably occupying their entire time during the period of the annual meeting."

Dr. Pepper reported that his Committee was not unanimous in its agreement that this plan is feasible, but that the Committee has presented the plan as a program for consideration. Having the examinations at the annual meeting will avoid the necessity of giving multiple examinations. An Associate would have an opportunity of taking the examination at the third, fourth or fifth anniversary of his Associateship and that during at least one of those years the annual meeting of the College would be in fair proximity to his residence. He further commented on the fact that these examinations would probably limit future membership largely to internists and pediatricians, because he could not visualize any examination which would be appropriate for internists, pathologists, roentgenologists, etc., alike.

Dr. Walter L. Bierring reported that the National Board of Medical Examiners have 50 or 60 on the Board, and that their examinations require two days and are divided into two sets. There was general discussion concerning the desirability of both a written and practical examination. President Meakins offered a brief discussion of the plan of the Royal College of Physicians. Dr. James Alex. Miller discussed the possibility of substituting an oral examination in the place of a practical examination. In further discussion, Dr. S. Marx White suggested the possibility of having the written examination at the annual meeting of the College and having the practical examination as a preliminary and regional matter preceding the written examination at the annual meeting.

President Meakins suggested that the examiners must be appointed by the Board of Regents and should hold office for at least five years on a rotating schedule; otherwise, there would be a variation of standards.

Dr. Musser, a member of the Committee, discussed the plan at some length, pointing out his belief that the plan should be put into effect, with the exception that candidates primarily would be younger men who have set their goal to become recog-

nized internists. He advised against postponement for another year. He pointed out that we have represented in the College membership the bulwark of the outstanding internists of this country. Those who are qualified but have not sought membership probably never would under the examination plan. Dr. Musser further pointed out that the examination could be outlined with a certain proportion of grades assigned to candidates for their record of what they have done, a certain proportion for the written examination and another proportion for the oral or practical part of the examination. If the College will establish a sound foundation for certifying qualified internists, it will have far reaching effect upon the appointments to staffs in hospitals, departments of internal medicine and other institutional positions. A plan should be adopted now, in the opinion of Dr. Musser, but the initiation of the examinations may be deferred for one year.

Dr. James Alex. Miller discussed the possibility of providing means for admitting a few outstanding men without examination. It was the consensus of opinion that the Regents and Officers of the College should busy themselves in inviting any such men who are not already Fellows to associate themselves with the College during the next year, preceding the initiation of the examination, and that after the examinations are actually initiated, no exception should be made.

Dr. Piersol, on behalf of the Committee on Credentials, reiterated the fact that the present method of admission to Fellowship on case histories, autopsies, publications, etc., is not satisfactory, and that the Committee will welcome some change in the way of an adequate criterion for election to Fellowship.

Dr. Ernest B. Bradley, also a member of the Committee on Credentials, expressed some doubt as to whether members of the College can be properly chosen on written examination alone. He did not believe that a man who has been out of medical school a long time, though he may be a recognized, good internist, can pass an examination as well as a young man just recently graduated. However, there is a necessity for some new plan of admission.

Dr. James Alex. Miller suggested the value of modifying present requirements by substituting the preparation of a thesis instead of the presentation of clinical reports and autopsies.

Dr. Walter L. Bierring discussed the different Boards established, in coöperation with the American Medical Association, for the different specialties, pointing out that there will be special boards for some of the specialties affiliated with internal medicine, and that the chief concern of the American College of Physicians should be "internal medicine."

Dr. Piersol then pointed out that the American College of Physicians should be the natural certifying board to work in coöperation with the American Medical Association in the certification of internists. The College should have a definite arrangement as the certifying body for internists, and the initiation of examinations at an early date will aid us in perfecting proper machinery for this plan.

Dr. Pepper inquired of the possibility of accepting roentgenologists, for instance, as members of the College on the basis of their certification by the certifying board for roentgenologists, indicating on his Fellowship Certificate of the College the basis for his election.

Dr. David P. Barr expressed grave doubts about putting into effect the recommendations of the Committee at the present time, due to the fact that there are among our members a few who are not primarily internists, and there are among those who are recognized internists some who are not members of the College. He expressed fear that some of these recognized internists who are not already members would not be impelled to join, particularly if examinations were put into their way for qualification. He expressed some doubt also concerning the feasibility of a written examination as being adequate to determine the qualifications of a candidate. He fur-

ther pointed out his agreement with Dr. Herrick that to attempt a practical examination without a large examining board would be unwise.

Dr. Herrick then suggested the postponement of final action on the matter until the April meeting, asking that the Committee be continued and be instructed to bring in a second report at that time. He said we have made remarkable progress today in educating ourselves as to what should be done. An important step of this character should not be taken by a single vote, but should be unanimous, after it has become perfectly clear what the College wants to do.

Dr. Pincoffs expressed the opinion that while it may not be desirable to come to a final decision at this meeting, something should be done without very much further delay. It would be a mistake to have the certification of internists initiated by some other agency than the College, for that would leave the College only important from the standpoint of its annual meeting, primarily, in the minds of many men. The purpose of Fellowship in the College should not simply be a certification of internists, but the establishment of a goal for which young men should work; something that will keep them studying and trying to improve and extend their qualifications.

Dr. S. Marx White expressed agreement with Dr. Pincoffs' opinions. He was sympathetic with Dr. Pepper concerning the need of breadth in the character of examinations. He said he was inclined to view this examination as a form of "graduate examination," and the certification of Fellowship as something comparable to it. The written examination should have only a small part in the determination of awarding graduate degrees. Attention should be given to the character of work the candidate has done; publications should have some definite recognition. If there is to be a certification of internists, that should be one of the chief functions of this College.

After further discussion, it was moved by Dr. Pepper, seconded by Dr. White, and regularly carried, that it be

Resolved, that the Board of Regents revoke its action of April 17, 1934, concerning the initiation of examinations for Associateship.

On motion by Dr. White, seconded by Dr. Stroud, and regularly carried, it was further

Resolved, that the report of the Committee on Examinations be accepted as one of progress, that the Committee be enlarged by the appointment of Dr. George Morris Piersol, as Chairman of the Committee on Credentials, and by Dr. Walter L. Bierring, from the standpoint of his experience with the National Board of Medical Examiners, and that the Committee be instructed to bring back a complete report at the meeting of the Board of Regents in April.

On motion by Dr. Pepper, seconded and regularly carried, it was

Resolved, that the College publish in the ANNALS of INTERNAL MEDICINE a report of progress in developing a plan for examinations to supplement the present plan of admitting members to the College, with the suggestion that the Editor prepare an editorial in the Annals expressing the consensus of opinion of the Board of Regents.

Dr. David P. Barr, Chairman of the Committee on the John Phillips Memorial Prize, discussed the deliberations of his Committee, and presented its recommendations. Inasmuch as the responsibility of the Committee had been extended to the selection of other awards than the John Phillips Prize the name of the Committee at present is inappropriate. Through the Executive Secretary and Dr. Pepper, a number of designs for the medal had been prepared and the Committee had decided that it would be appropriate to use the head of "Laennec," as representative of Internal Medicine, on this medal. The Committee had recommended that the wording on the medal be restricted. It should primarily be the award of the American College of Physicians, known as the John Phillips Memorial Award. The medal should bear the Seal of the College and the name of the recipient and the year of the award should

be engraved on the outside edge of the medal. The Committee recommended a medal three inches in diameter and presented a sample for size.

Dr. Barr explained that the Committee had communicated with some 40 men, including many members of the Board of Regents, asking for suggestions concerning recipients for the award for 1935. A large number of candidates had been so obtained. The Committee had selected the recipient recommended from this group, after taking the position that it could not afford to sponsor new work which had not been completely verified, but rather that the award should be offered to a man of long standing achievement in the medical sciences, and one whose work at the present time is active and important.

The Committee also raised the question of how the Research Fellow should be selected for next year, and suggested that letters be written within one month to all the Professors of Medicine and Pediatrics in the country and to all members of the Board of Regents, asking for suggestions as to likely candidates. It had been thought last year that the machinery of the National Research Council could be used. The Committee wants to receive all these suggestions, and, if necessary, utilize the machinery of the National Research Council as well. If a candidate is proposed and is acceptable and worthy in every respect, it would not be necessary to resort to the National Research Council. If we cannot obtain a worthy candidate, the National Research Council will be very glad to present several of their candidates for our consideration. It is thought wise to use a form of application and recommendation similar to those used by the Research Council.

(To be continued)